Reactions of Coordinated Ligands and Homogeneous Catalysis

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PREFACE

Early in the history of complex inorganic compounds, it was recognized that the properties of some nonmetallic substances are greatly altered by combination with metallic salts. Early examples are found in the tanning of animal hides by reaction with chromic salts and the stabilization of azo dyes by metallation.

In his "Neuere Anschauungen auf dem Gebiete der Anorganischen Chemie," Werner mentioned several examples of such alteration in properties, and he and his students discovered several examples of ligand reactions, but these phenomena do not seem to have greatly impressed him. They were much less important, in his thinking, than the behavior of the coordinated metal and the nature of the metal-ligand bond.

Other coordination chemists, following Werner's lead, have pointed out, over and over, that when a metallic ion is coordinated, its color is changed, the solubility of its salts is altered, and the basicity of its hydroxide is increased, but few have observed that the properties of the ligand are affected just as fundamentally as are those of the metallic ion. It is apparent to all that the volatility of ammonia, the basicity of the hydroxide ion, and the toxicity of the cyanide ion are greatly decreased when these groups attach themselves to metal ions, but such changes have seldom been stressed. Perhaps, with these simple ligand groups, the changes have seemed too obvious to need mention, but they should have suggested, many years ago, that study of the behavior of coordinated groups would be both interesting and rewarding.

Since coordination chemistry has been considered to be a branch of inorganic chemistry, its devotees have not been interested as much in the study of organic ligands as of the metals, and the behavior of ligands has not attracted much attention. Recently, however, several developments have directed our thoughts to this as a promising field for investigation; research in biochemistry has shown the importance of coordinated metal ions in biochemical synthesis and in energy storage and transfer, the search for polymers that can withstand high temperatures has led to the study of a variety of interesting ligand reactions, and the discovery of the oxo- and the Ziegler-Natta catalytic syntheses has drawn attention to the role of coordination compounds as reaction intermediates.

These, and other similar, developments have suggested the possibility of controlling the course of organic syntheses and the nature of the products by coordinating the reactants with metal ions. Several striking successes have been achieved; others are in process of development; still others, no doubt, will follow. The symposium upon which this book is based was therefore most timely, and its publication is an important step in the history of coordination chemistry. It should stimulate a great deal of interesting research.

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Reactions of Ligands in Metal Complexes

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The catalytic and other chemical effects of metal ions on reactions of organic molecules are recognized in a number of classes of systems: catalysis of nucleophilic reactions, reactions of alkenes and alkynes, stereospecific polymerization, aromatic substitution reactions of metalcyclopentadienyl compounds and metal ion effects in biological systems. The fundamental aspects may be studied most directly and in greatest detail in systems designed to retain the ligand in the coordination sphere of the metal ion during and after the chemical reaction. The presence of the metal ion may lead to conjugative and inductive electronic effects, special steric effects, specific protective action, and novel energy transfer phenomena. Organic molecules not otherwise stable may be produced, and the metal ion may serve as a template to hold reactive groups in position for sterically highly selective multistep reactions.

The reactions of metal complexes may be grouped into the following categories:

1. Substitution or Addition at the Central Metal Atom

$$[M(A)_m] + B \rightarrow [M(A)_{m-1}B] + A$$

$$[M(A)_m] + nB \rightarrow [M(A)_m(B)_n]$$

2. Intramolecular Isomerization

$$d - [M(AA)_3] \rightleftharpoons l - [M(AA)_3]$$

3. Oxidation-Reduction of the Central Metal Atom

$$[M(A)_m]^{n+} \rightarrow [M(A)_m]^{(n+1)} + e^-$$

4. Reactions of the Coordinated Ligand

$$[M(A)_m] + C \rightarrow [M(A)_{m-1}D] + E$$

The first three categories constitute the traditional chemistry of coordination compounds and these continue to be studied in great detail. They are discussed at length in many excellent reviews, reference books, and texts published within the past five years. In contrast, category 4 has not been widely recognized. In fact, it is appropriate to describe the meaning of the equation representing category 4 in more detail. A complex ion (or molecule), containing a number of groups A (*m* being equal to the coordination number), reacts with a reagent, C. Reagent C transforms one (or more) of the ligands into a new species, D, that product remaining coordinated to the metal ion, M. Product E represents the transformed reagent. In essence, a ligand reaction involves chemical transformation of the ligand while it remains coordinated to a metal ion.

The relatively scanty information available and the limited research effort devoted to the study of ligand reactions cannot be attributed to the relative youth of the experimental area, for the literature contains scattered observations dating back to the earliest possible time at which such reactions could be recognized. Indeed, Werner (*68*, *76*) utilized a ligand reaction in his classic demonstration of the manner of attachment of thiocyanate to cobalt(III). In his view, the conversion of thiocyanate to ammonia within the coordination sphere could only mean that SCN$^-$ is attached to cobalt through the nitrogen atom (Equation 1).

$$(NH_3)_5Co(NCS)^{+2} \xrightarrow[\text{oxidation}]{\text{hydrolytic}} (NH_3)_5Co{-}NH_3{}^{+3} \qquad (1)$$

Similarly, in 1929, Chernyaev (*14*) reduced the coordinated nitro group to ammonia.

$$[Pt(en)(NH_3)(NO_2)]Cl \xrightarrow[\text{HCl}]{\text{Zn}} [Pt(en)(NH_3)_2]Cl_2 \qquad (2)$$

In a number of classes of systems, the catalytic and other chemical effects of metal ions on reactions of organic and inorganic molecules are generally recognized: the catalysis of nucleophilic reactions such as ester hydrolysis; the reactions of alkenes and alkynes in the presence of metal carbonyls (*8*, *9*, *69*); stereospecific polymerization in the presence of Ziegler catalysts (*20*, *55*, *56*); the activation of such small molecules as H_2 (*37*), O_2 (*13*), H_2O_2 (*13*), and possibly N_2 (*58*); and aromatic substitution reactions of metal-cyclopentadienyl compounds (*59*, *63*).

The fundamental aspects of metal ion effects may be studied most directly and in greatest detail in systems designed to retain the ligand in the coordination sphere of the metal ion during and after the chemical reaction. Specific examples of systems of this kind cover a much broader range of organic and inorganic ligands than is implied by the most familiar examples. The presence of the metal ion may lead to a variety of conjugative and inductive electronic effects, special steric effects, specific protective action, and novel energy transfer phenomena. Organic molecules that are not otherwise stable may be produced, and the metal ion may serve as a template to hold reactive groups in proper position for sterically highly selective, multistep reactions.

Active Areas of Research Related to Ligand Reactions

Catalysis of Nucleophilic Substitution Reactions. It has been known for many years that metal ions with a strong affinity for halogens will accelerate the reactions of alkyl halides with nucleophiles (Equation 3). It is assumed that the polarization of the carbon-halogen bond, as a consequence of coordination,

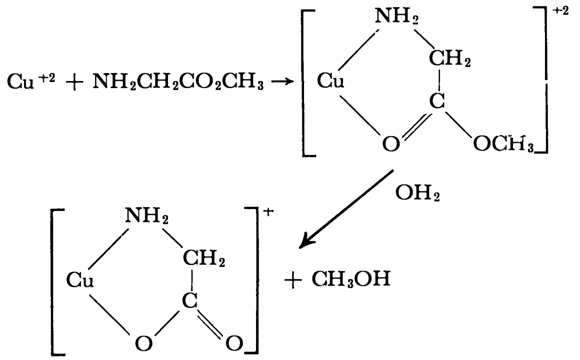
$$RCH_2X + B \xrightarrow{Ag^+} RCH_2B + AgX \qquad (3)$$

is responsible for this effect (Equations 4 and 5).

$$RCH_2X + Ag^+ \rightarrow R\overset{\delta+}{C}H_2—\overset{\delta-}{X}...Ag^+ \qquad (4)$$

$$R\overset{\delta+}{C}H_2—\overset{\delta-}{X}...Ag^+ + B \rightarrow RCH_2B + AgX \qquad (5)$$

Similarly, the rates of hydrolysis of amino acid esters are enhanced by the presence of metal ions (Equation 6) (*6, 7, 48, 77*).



(6)

Reactions of Alkenes and Alkynes in Presence of Metal Carbonyls. Metal carbonyls—e.g., $Ni(CO)_4$, $Fe(CO)_5$, and $Co_2(CO)_8$—and hydrocarbonyls—$HCO(CO)_4$ and $H_2Fe(CO)_4$—act as catalysts for the transformation of simple unsaturated materials into a wide variety of larger molecules. Perhaps the simplest example is that of hydroformylation (Equation 7). Reppe chemistry

$$H_2C{=}CH_2 + H_2 + CO \xrightarrow{\text{catalyst}} CH_3CH_2CHO \qquad (7)$$

reveals a great variation in the products obtained from the reactions of acetylenes with other simple substances under the influence of carbonyl catalysts. For example, the formation of cyclo-octatetraene, unsaturated aldehydes, esters, and nitriles, hydroquinones, cyclopentadienones, and benzenes may be typified by Equations 8 and 9.

$$HC{\equiv}CH \xrightarrow{\text{catalyst}} C_8H_8 \qquad (8)$$

$$RC{\equiv}CH + H_2 + CO \xrightarrow{\text{catalyst}} RHC{=}CHCHO \qquad (9)$$

In modern terms, one can begin to understand such processes only on the basis of the manner in which the simple reactant molecules combine with the metal atom of the catalyst, for the reactants must become bound to these species in order to respond so profoundly to the influence of the metal compounds. In recent years the isolation and characterization of a wide variety of organic derivatives of metal carbonyls have substantially improved the understanding of these processes (*8, 9, 69*). Some of these new compounds appear to be intermediates in previously discovered catalytic processes, while others may be utilized to obtain new and unusual products from such systems. One of the first types of intermediates to be isolated from systems of this class is exemplified by the substance of the formula $Fe_2(CO)_6-(C_6H_5C{\equiv}CC_6H_5)_2$. Strong evidence exists for the structure given in Figure 1. The structure is not an expected one; however, it reflects properties of some generality. Treatment of this material with various reagents leads to the production of structurally related materials, a number of them being heterocyclic compounds with structures readily traceable to the intermediate.

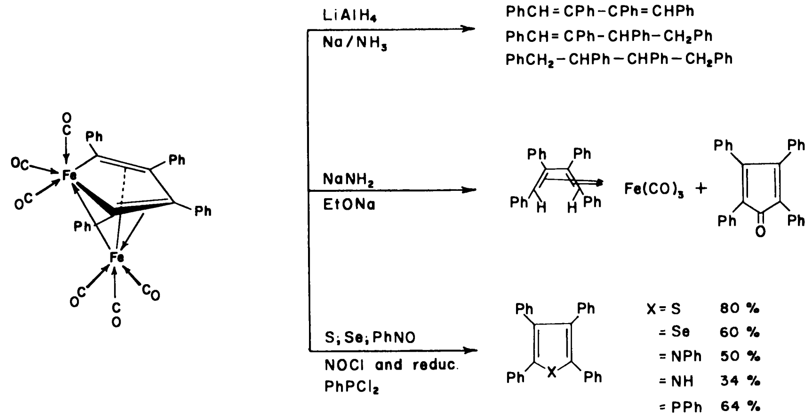
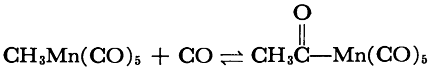


Figure 1. *Structure and reactions of $Fe_2(CO)_6(PhC \equiv CPh)_2$*

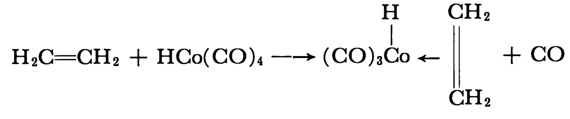
Perhaps the most significant reaction of this class to be discovered and characterized is the carbonyl insertion reaction (Equation 10) (*15*). As indicated, the methyl group (or other sigma-bonded organic group) is converted into an



$$CH_3Mn(CO)_5 + CO \rightleftharpoons CH_3\overset{\overset{\displaystyle O}{\|}}{C}{-}Mn(CO)_5 \qquad (10)$$

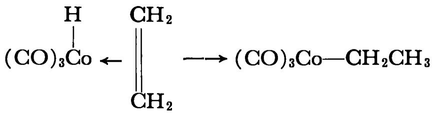
acyl group by insertion of a carbon monoxide molecule between the alkyl group and the metal atom. The process is reversible under known conditions and the corresponding reaction has also been established for the cobalt system, $CH_3Co(CO)_4$. The delineation of this elementary process provides a basis for understanding the carbonylation reactions and processes which extend the carbon chain.

The hydroformylation reaction may be explained (formally) as proceeding through three steps (*8*, *69*)—formation of a metal-carbon sigma bond, carbonyl insertion, and addition of H_2, or some other material containing labile hydrogen, across the metal-carbon bond. The reaction of an olefin with a metal complex should proceed through coordination by means of the pi-electrons of the olefin, forming a well known type of linkage (Equation 11).



$$H_2C{=}CH_2 + HCo(CO)_4 \longrightarrow (CO)_3\overset{\overset{\displaystyle H}{|}}{Co} \leftarrow \begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + CO \qquad (11)$$

The shift of the hydrogen atom to the olefin, accompanied by rearrangement of the Co-olefin bond to a link of the more common sigma type, is presumed to proceed in analogy to the addition of other molecules of the form HX across a double bond (Equation 12).



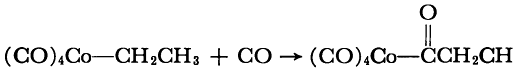
$$\overset{\displaystyle H}{\overset{|}{(CO)_3Co}} \leftarrow \begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} \longrightarrow (CO)_3Co{-}CH_2CH_3$$

(12)

This material is electron-deficient and will absorb carbon monoxide (Equation 13).

$$(CO)_3Co{-}CH_2CH_3 + CO \rightarrow (CO)_4Co{-}CH_2CH_3 \qquad (13)$$

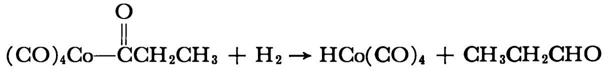
Equations 11, 12, and 13 constitute a process for the formation of the metal-carbon sigma bond. Carbonyl insertion may now occur as shown in Equation 14.



$$(CO)_4Co{-}CH_2CH_3 + CO \rightarrow (CO)_4Co{-}\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_3$$

(14)

The reaction may then be consummated by the addition of hydrogen to form the product and regenerate the catalyst (Equation 15) (*44*).



$$(CO)_4Co{-}\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_3 + H_2 \rightarrow HCo(CO)_4 + CH_3CH_2CHO$$

(15)

The examples chosen in connection with the reactions of alkenes and alkynes in the presence of metal carbonyls illustrate a number of the factors pertinent to the general realm of ligand reactions.

Identification of elementary processes involving coordinated reactive groups leads to broad understanding.

Isolation of reactive intermediates provides the basis for identification of such elementary processes.

Metal ions may be expected to combine simple molecules into higher molecular weight species well suited to coordinate to the metal ion.

The maximum amount of information will be obtainable in cases where the species of interest remains bonded to the metal ion during the course of the transformation.

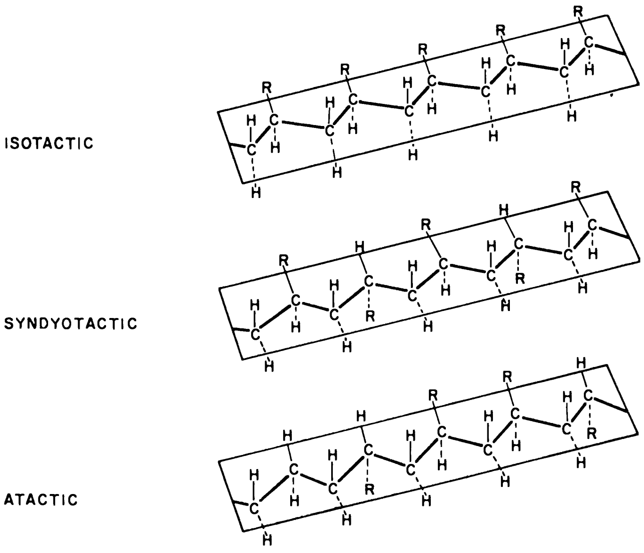
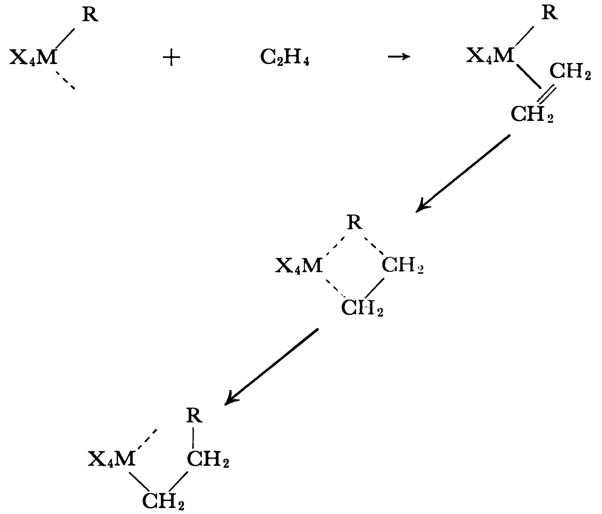


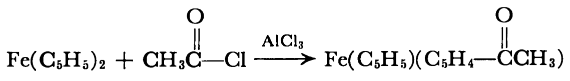
Figure 2. Stereoisomers of vinyl polymers

Stereospecific Polymerization of Alpha-Olefins. Certain combinations of metal alkyls and transition element compounds serve as catalysts for the polymerization of such α-olefins as propylene and styrene into final products of highly ordered structure (*55*, *56*). The substituent groups (CH_3 or C_6H_5) on the resulting polymer may all be oriented in the same way (isotactic) or may have opposite orientations (syndiotactic). In the absence of the action of a stereospecific catalyst, the substituents are oriented at random (atactic) (Figure 2). This increased order in the molecular structure of the polymer molecules facilitates crystallization and greatly improves physical properties. These Ziegler-Natta catalysts also facilitate polymerization at lower temperatures and pressures than is possible by other methods. Certain aspects of the mechanism almost certainly resemble corresponding processes in other olefin or acetylene reactions (Equations 11 and 12). A simplified view (*20*) of the propagation reaction is represented in Equation 16.



(16)

Aromatic Substitution Reactions of Metal-Cyclopentadiene Compounds. The behavior of ferrocene, bis(cyclopentadienyl)iron(II), as an aromatic molecule under conditions for electrophilic substitution has received much attention by both organic and inorganic chemists (*59*, *63*). The Friedel-Crafts acylation may illustrate the reactivity of this very stable compound.



$$Fe(C_5H_5)_2 + CH_3\overset{\overset{O}{\|}}{C}—Cl \xrightarrow{AlCl_3} Fe(C_5H_5)(C_5H_4—\overset{\overset{O}{\|}}{C}CH_3)$$

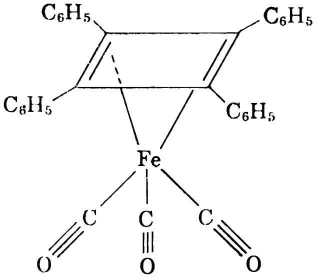
(17)

More recently, a number of other pi-complexes have been shown to undergo reactions typical of aromatic systems.

Although the few examples cited above are thoroughly inadequate to convey the magnitude of very recent research efforts dedicated to the few areas mentioned, they have been discussed to emphasize the potentialities of the total field of metal ion effects on the reactions of other substances, and, particularly, to emphasize the significance of the otherwise scantily studied realm of ligand reactions. Many beginnings exist for the development of areas of chemistry which may grow into fields of comparable magnitude and significance to the few mentioned above. For example, although it is currently less in vogue to study such processes in aqueous media, their elucidation should have far greater significance in the unraveling of the chemistry of living systems than is true of areas of more vigorous current investigation. A number of metal ion effects are manifest in certain of the examples to be cited.

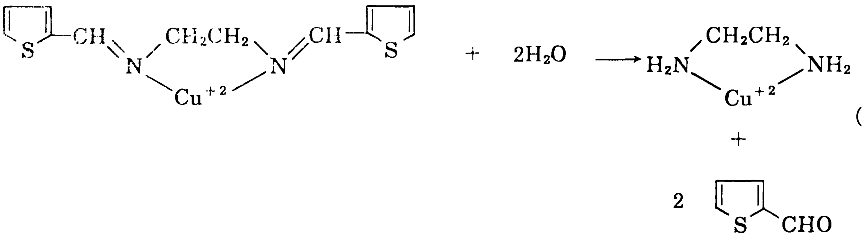
Areas for Future Development

Stabilization of Organic Species through Chelation or Complexation. The most quoted example of this phenomenon involves the stabilization of cyclobutadiene (*22, 41, 52*) in complexes such as



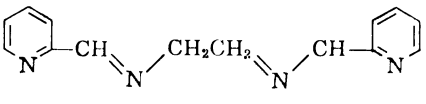
This and similar examples are dramatic in revealing the great ability of metal ions to stabilize unknown organic molecules through coordination.

A number of observations show the profound effect of chelation on the stability of Schiff bases and similar unsaturated nitrogen-containing ligands. Eichhorn and coworkers found that the Schiff base of bis(thiaphenal)ethylenediimine is hydrolyzed in the presence of Cu^{+2}, with the formation of the ethylenediamine complex (Equation 18) (*26, 28*).

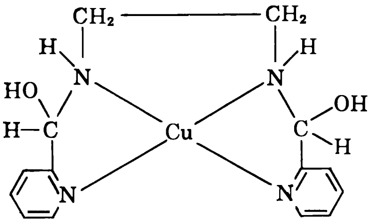


(18)

The –S—C—C=N— chelate ring is greatly weakened or does not tend to form for steric reasons and the electron-withdrawing effect of the metal ion coordinated to the nitrogen atom facilitates nucleophilic attack at the imine carbon atom. Similar observations have been made with bis(2-pyridinal)ethylenediimine

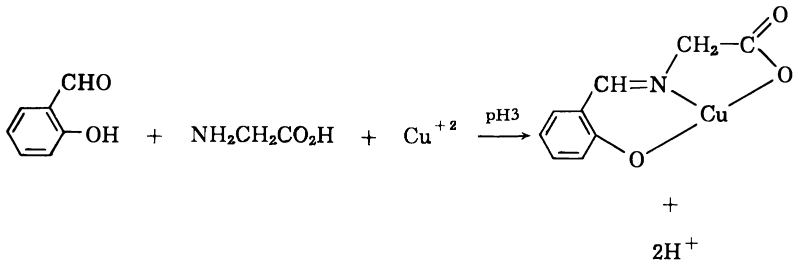


which would form chelate rings of approximately the same size (*11*). It was found that the iron(II) complex hydrolyzes at a measurable rate in dilute solutions. An intermediate hydrolysis product has been isolated in the case of the copper complex (*11*).



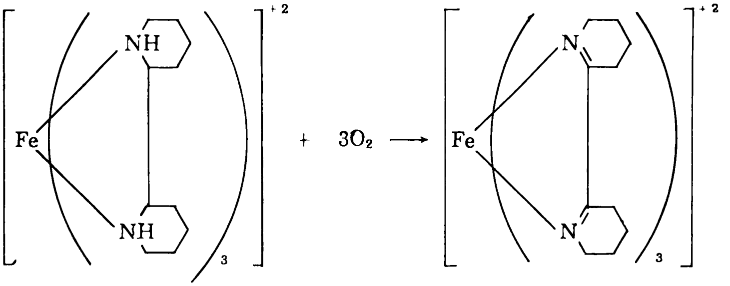
Presumably, saturation of the C=N link relieves the strain in the chelate ring.

On the other hand, Eichhorn (*27, 57*) has shown that the Schiff base of salicylaldehyde with glycine is stabilized by chelate formation at pH values where the free ligand is readily hydrolyzed.



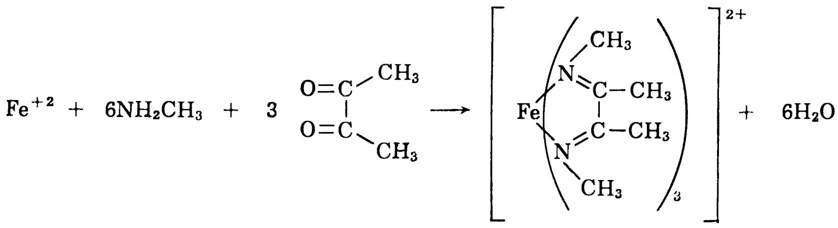
(19)

Perhaps the most interesting example of this phenomenon is related to the dehydrogenation of bipipyridine in the presence of iron(II) (Equation 20) (*49*).



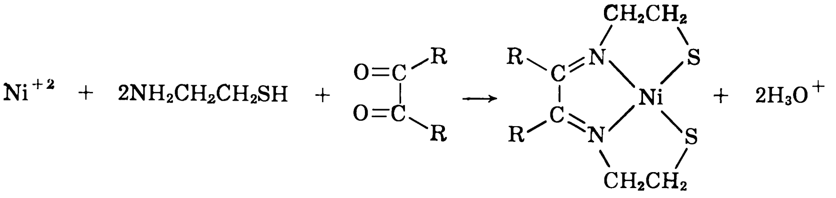
(20)

The very great stability of the iron(II) —N=C—C=N— chelate ring provides the driving force for the reaction. This is further illustrated by the formation of monomeric Schiff bases between α-diketones and methylamine (Equation 21), for in the absence of the metal ion (Fe^{+2}, Co^{+2}, Ni^{+2}) polymeric condensation products are formed (*30, 49*).



(21)

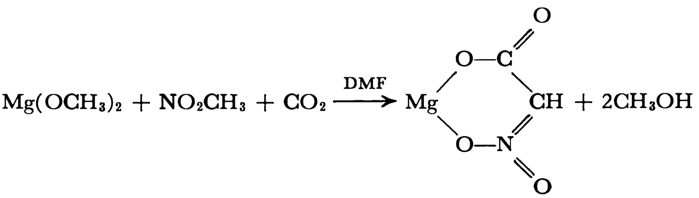
This principle has recently been applied to synthesize the planar complexes of the Schiff bases formed between β-mercaptoethylamine and α-diketones (Equation 22) (*73*).



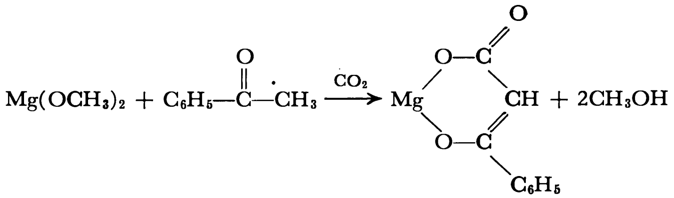
(22)

In the absence of the metal ion, thiazolines and mercaptals are formed.

Stiles and coworkers (*70*) have taken advantage of the effect of chelation to carboxylate compounds having active methylene groups. The reactions of these substances with CO_2 in the presence of aluminum or magnesium alkoxide readily produce chelate products (Equations 23 and 24).

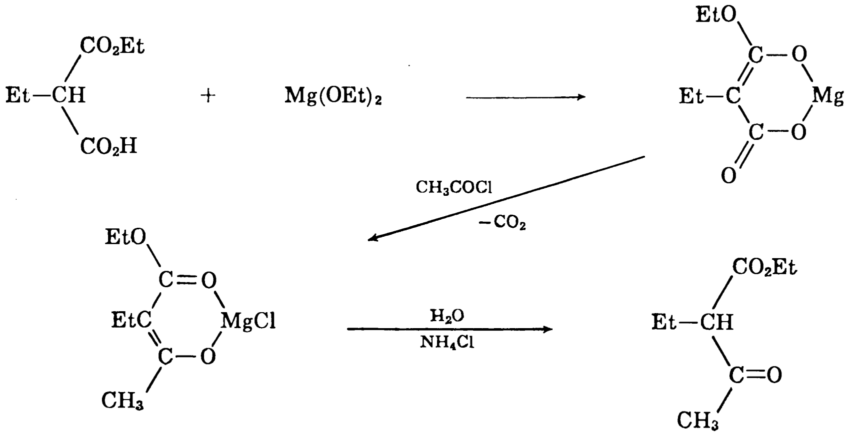


(23)



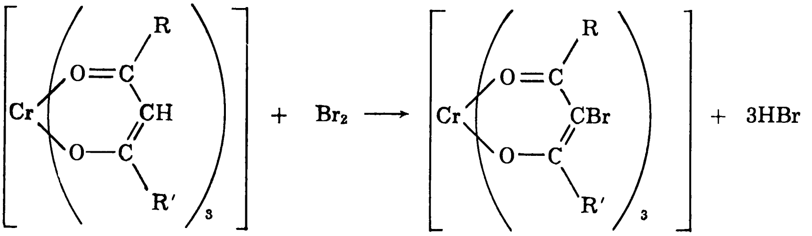
(24)

Closely related to the carboxylation reactions is the reported preparation of β-ketoesters and β-diketones by replacement of CO_2 with acyl functions in magnesium derivatives of malonates (Equation 25) (*42*).



(25)

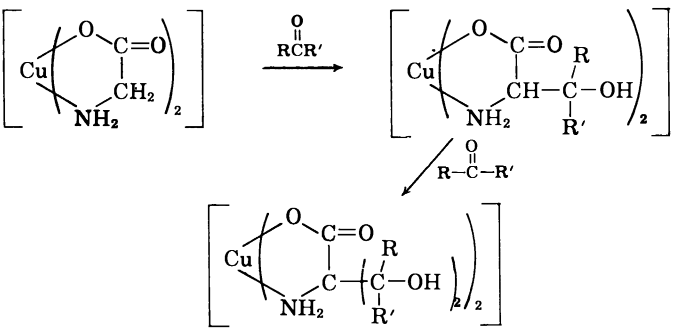
Reactions of Nondonor Chelate Ring Member in the Intact Ring. In some cases, chelate ring members will react without impairment of the stability of the complex. The most studied example involves substitution at the central carbon atom in β-diketone complexes (*16–19, 21, 45, 64*). This is illustrated with the bromination reaction in Equation 26. Acylation, formylation, and nitration reactions have also been carried out.



(26)

Similar reactions occur with M = Al^{+3}, Co^{+3}, Fe^{+3}, Ga^{+3}, Sc^{+3}, Cu^{+2}, and VO^{+2} using ICl, *N*-bromosuccinimide, *N*-chlorosuccinimide, and *N*-iodosuccinimide.

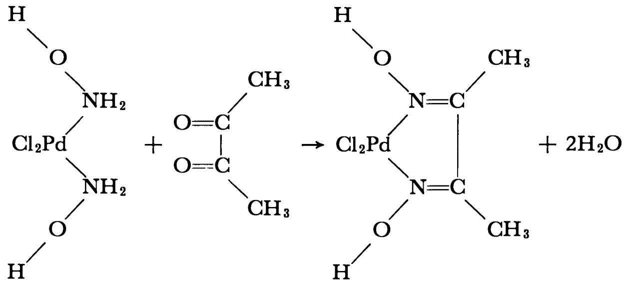
It has also been shown that the α-methylene group in chelated glycine will undergo substitution. The reaction of the copper(II)-glycine complex with ketones or aldehydes produces β-hydroxyamino acids (Equation 27) (*1, 65*).



(27)

In this case, coordination of the ligand to the metal ion renders the amino group relatively unreactive, thus limiting competitive reaction due to that functional group. This is a point for further discussion.

Reactivity of Coordinated Donor Atom or Functional Group. The significance of metal complexes of ammonia and the amines in the continuing development of coordination chemistry naturally leads to questions relating to the reactivity of the coordinated NH_3 molecule in particular and the coordinated NH_2— group in general. As Equation 27 suggests, the coordinated NH_2 group is not highly reactive toward condensation with ketones and aldehydes; however, recent work suggests that coordinated hydroxylamine may combine with α-diketones to form α-dioximes *in situ* (Equation 28) (*23*).



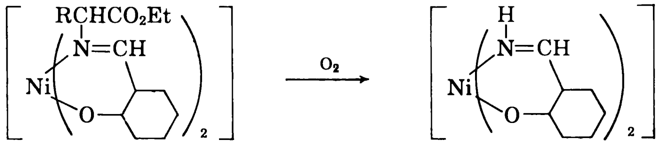
(28)

The coordinated amino group is insensitive to the action of acyl halides under moderate conditions. The best defined reaction (*75*) of the group is acid dissociation and this phenomenon has been observed for a broad span of compounds—for example,

$$(NH_3)_4ClPtNH_3^{+3} + OH^- \rightarrow (NH_3)_4ClPtNH_2^{+2} + H_2O \qquad (29)$$

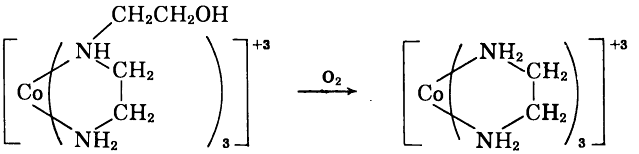
The conjugate base in such an equilibrium should exhibit a significant tendency to act as a nucleophile toward a variety of reagents.

Under oxidative conditions, a side chain alkyl group is sometimes removed from a coordinated amino group. This has been observed in the case of the complexes of the Schiff base of salicylaldehyde with alanine esters (Equation 30) (*60, 61*).



(30)

A similar reaction is observed with the Cu^{+2} complex. No reaction occurs with glycine esters. A similar reaction occurs when cobalt(III) complexes are prepared from solutions of hydroxyethylethylenediamine and similar ligands (*24, 25*). The chelate ring-forming portion of the complex remains intact; however, the products derived from the oxidized hydroxyethyl group appear complicated.



(31)

A number of compounds containing phosphorus-metal bonds exhibit an interesting reactivity. In platinum(II) complexes, coordinated PCl_3 undergoes solvolysis reactions with water and alcohols to form stable orthophosphite esters or phosphorous acid (Equation 32) (*66, 67*).

$$[PtCl_2(PCl_3)_2] + 6\ ROH \rightarrow [PtCl_2\{P(OR)_3\}_2] + 6\ HCl \qquad (32)$$

where R = alkyl group or hydrogen.

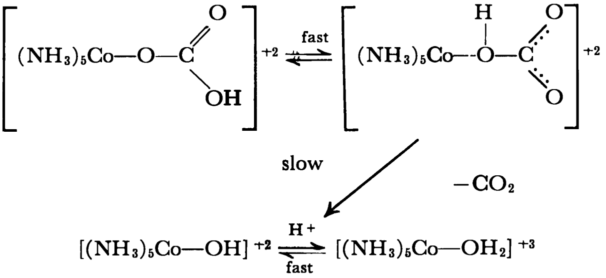
The gold compound $AuCl(PCl_3)$ also forms stable solvolysis products from alcohols; however, reduction occurs in water (*2*, *51*). Surprisingly, it has been reported that the iridium compound $IrCl_3(PCl_3)_3$ does not solvolyze in alcohols (*35*, *70*).

$$[AuCl(PCl_3)] + 3ROH \rightarrow [AuClP(OR)_3] + 3HCl \qquad (33)$$

where R = alkyl group only.

The reactivities of such molecules should reflect the effect of the metal ion on the electron density at the phosphorus atom.

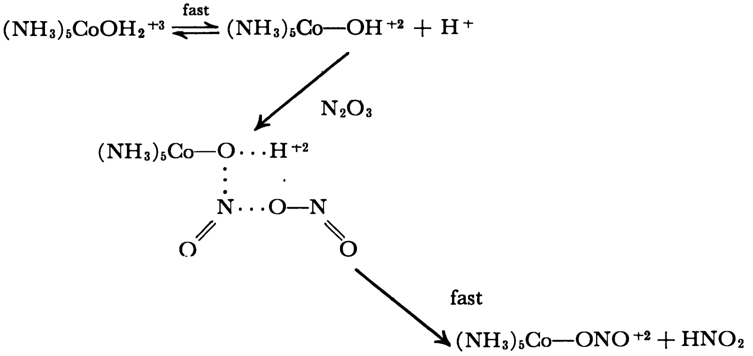
In certain instances, the coordinated oxygen atom may undergo reaction. The complete and elegant work carried out on carbonato–ammine complexes of cobalt(III) illustrates this situation. As Equation 34 reveals, the acid hydrolysis of $[(NH_3)_5CoCO_3]^+$ involves substitution at the carbon-oxygen bond, rather than the cobalt-oxygen bond (*4*).



(34)

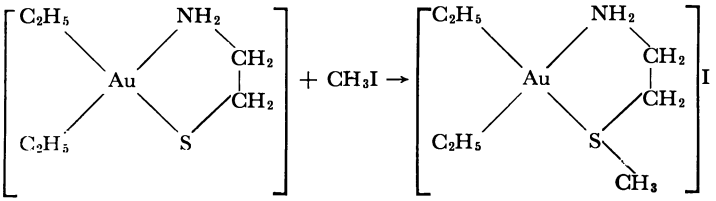
Isotopic enrichment experiments proved the point of cleavage.

The formation of nitrito complexes provides a similar example, involving addition at the coordinated oxygen atom (Equation 35) (*5*).



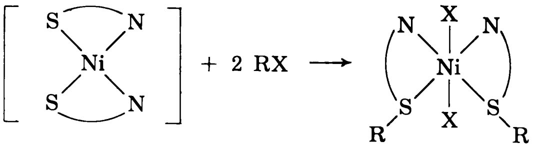
(35)

Ewens and Gibson (*29*) reported an early observation on the reaction of the coordinated sulfur atom as a nucleophile (Equation 36), showing the conversion of the mercaptide ion to a thioether function within the coordination sphere.



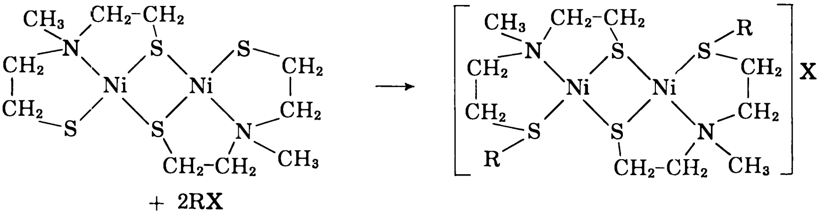
(36)

These observations have been extended to complexes of mercaptoamines with nickel and palladium, the simplest reaction being as shown in Equation 37 (*12*, *43*) (where $N \frown S$ represents $NH_2CH_2CH_2S^-$).



(37)

The reaction represents an energy transfer process, for the very strong Ni—S—R bond is replaced by the relatively weak nickel-thioether link. This is sharply emphasized by transformation of the nickel from the square planar (diamagnetic) form (which it assumes with strong ligands) to the paramagnetic product. Similarly, in the palladium case the impaired complexing ability resulting from the ligand reaction is reflected by transformation of the neutral complex $Pd(NH_2CH_2CH_2S)_2$ into $Pd(NH_2CH_2CH_2S{-}R)X_2$, for the halides exhibit sufficient coordinating ability to displace one mole of converted ligand. Terminal mercaptide groups exhibit a greater tendency to act as nucleophiles than bridged groups.



(38)

Kinetic studies on the latter reaction reveal unusually low activation energies and frequency factors, an observation consistent with pre-equilibrium coordination of the alkyl halide to the metal atom (*12*). (L is the ligand given in Equation 38.)

$$\begin{tikzcd}
{[Ni_2L_2] + RX} \arrow[r, shift left, "\text{fast}"] & {[Ni_2L_2\cdot RX]} \arrow[l, shift left] \arrow[dl, "\text{slow}"] \\
{[Ni_2(L)(L{-}R)]X} &
\end{tikzcd} \qquad (39)$$

The nucleophilic power of a sulfide group is greatly impaired by replacing the nickel ion by palladium.

Reactions at α-Position. Many studies have been concerned with the reactions of alkyl halides with cyanide in the presence of various metal ions, and with the direct alkylation of cyanide complexes. The classic synthesis of isonitriles was accomplished by the use of silver cyanide, whereas the corresponding reaction of organic halogen compounds with alkali cyanides yields nitriles (Equations 40 and 41) (*34*, *36*).

$$NaCN + RX \rightarrow R{-}CN + NaX \qquad (40)$$

$$AgCN + RX \rightarrow R{-}NC + AgX \qquad (41)$$

The product of Equation 41 is generally of the form RNC—AgX. A recent review of isonitrile complexes (*53*) reveals that all the entries in Table I form such species, and that all those not circled may be prepared by direct alkylation of the corresponding cyanide complex. Some typical reactions illustrating the thoroughness of the early work are given by Equations 42 (*33*), 43, and 44 (*38, 39, 40, 61*).

Table I. Elements Forming Isonitrile Complexes by Direct Alkylation (53)

IB	*IIB*	*VIA*	*VIIA*	*VIII*		
Cu	Zn	Cr	Mn	Fe	Co	Ni
Ag	Cd	Mo	–	Ru	Rh	Pd
Au	Hg	W	Re	–	–	Pt

$$Ag_4Fe(CN)_6 + 4C_2H_5I \rightarrow [Fe(CNC_2H_5)_4(CN)_2] + 4AgI \qquad (42)$$

$$K_4Fe(CN)_6 + 3(CH_3)_2SO_4 \rightarrow [Fe(CNCH_3)_6]^{+2} + 3SO_4^{-2} + 4K^+ \qquad (43)$$

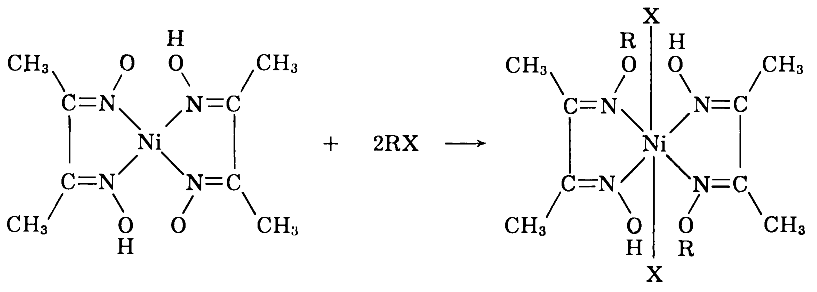
$$\begin{tikzcd}
{[Fe(CNCH_3)_6]Cl_2} \arrow[r, "130\text{–}150^\circ\text{ C.}", "\text{vacuo}"'] & {\begin{array}{c}[Fe(CNCH_3)_4(CN)_2] + 2CH_3Cl \\ (\alpha\text{ and }\beta\text{ forms})\end{array}} \arrow[dl, "CH_3I"] \arrow[d, "C_2H_5I"] \\
{[Fe(CNCH_3)_6]I_2} & {\alpha\text{- and }\beta\text{-}[Fe(CNCH_3)_4(CNC_2H_5)_2]}
\end{tikzcd} \qquad (44)$$

In the case of these reactions, the formation of isonitriles may be ascribed to the protective action of the metal ion, for cyanide complexes of the metals invariably involve a carbon-metal bond, leaving only the terminal (alpha) nitrogen atom to act as a nucleophile toward an external reagent. The great generality of this particular ligand reaction may be related to the fact that the ligand produced exhibits complexing power of magnitude and type similar to that of cyanide ion. Consequently, large amounts of energy are not stored in the metal ligand bond during the course of the ligand reaction. Recent work (*40*) reveals that the isonitrile complexes formed from α-phenyl alkyl halides may undergo electrophilic substitution at the phenyl group. Bromination, nitration, alkylation, and sulfonation reactions have been carried out.

$$[(C_6H_5CH_2NC)_5FeCN]^+ \xrightarrow[H_2SO_4]{HNO_3} [(O_2NC_6H_4CH_2NC)(C_6H_5CH_2NC)_4FeCN]^+ \qquad (45)$$

$$[(C_6H_5CH_2NC)_5FeCN]^+ \xrightarrow[H_2SO_4]{20\%\ SO_3} [(HO_3SC_6H_4CH_2NC)_5FeCN]^+ \qquad (46)$$

An additional example of a functional group undergoing reaction at the alpha atom is provided by the reactions of coordinated oximes. The earliest observation on this class of system appears to have been reported by Barker who reacted bis(dimethylglyoxime)nickel with methyl iodide and dimethyl sulfate (*3*). The formulations suggested for the products are archaic; however, the experiments have been repeated and found to be substantially correct (*31*). The reactions are exemplified in Equation 47.



(47)

As in the case of the reactions of the coordinated RS^- group, alkylation results in a weakening of the complexing ability of the ligand as evidenced by an expansion of the coordination number of the nickel ion. Similar reactions have been carried out with the complexes of palladium and platinum, and with all three metals and 2-pyridinaldoxime (POX). In the cases of palladium and platinum, one mole of coordinated ligand tends to be displaced by halide ions (Equation 48).

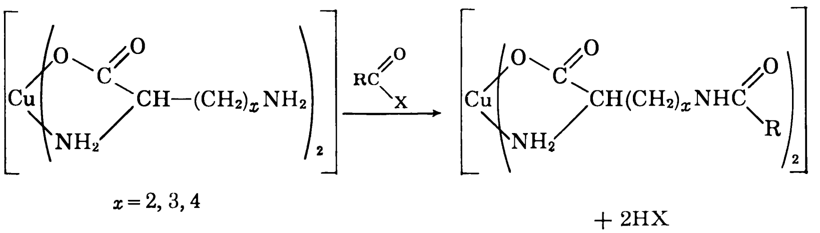
$$[Pd(POX)_2] + 2C_6H_5CH_2Br \rightarrow [Pd(POX{-}CH_2C_6H_5)Br_2] + POX{-}CH_2C_6H_5 \qquad (48)$$

The results of acylation reactions with dimethylglyoxime reveal that ligand displacement invariably occurs (Equation 49) (*47*),

$$[M(DMG)_2] + 2CH_3COCl \rightarrow [M(HDMG)Cl_2] + DMG(COCH_3)_2 \qquad (49)$$

where M = Ni(II), Pd(II), or Pt(II).

Reactions of Terminal Groups. Some 25 years ago, Kurtz (*50*) made the very reasonable assumption that coordination to an amino group might protect that group under conditions which would lead to the reaction of other amino groups in the same molecule. His successful application of this idea is illustrated in Equation 50.

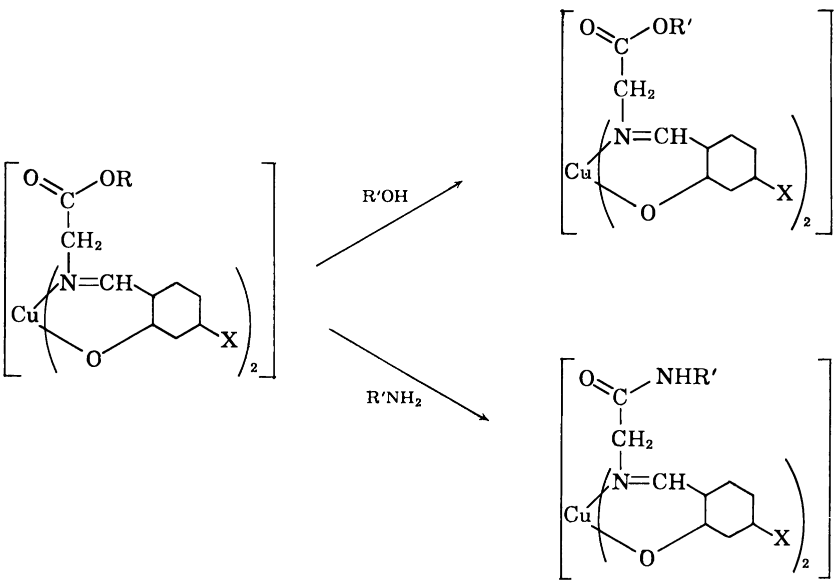


(50)

Repetition and modification of his procedures have both confirmed this work and led to the possibility that the technique may be utilized to determine the mode of coordination of polydentate ligands containing amino groups (*10*).

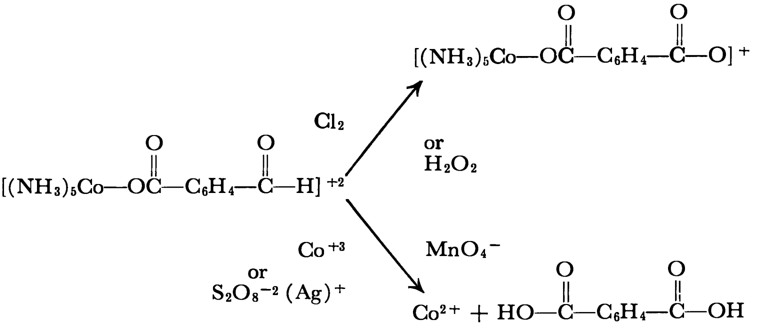
The apparent simplicity and virtual certainty of Kurtz' assumption are somewhat clouded by results obtained on complexes of hydroxyethylethylenediamine and similar ligands, for determined efforts have failed to reveal any of the normal reactions on the part of the free alcoholic function in complexes of cobalt(III) with these ligands (*24*, *25*). In contrast, Krause and Goldby have esterified the free hydroxyethyl group in bis(2-hydroxyethyliminodiacetato)chromate(III) (*46*).

The behavior of a free terminal carboxyl group appears to parallel that of the amino group more closely. Ester exchange and amide formation have been observed for such groups (Equation 51) (*54*, *61*, *74*).



(51)

An interesting kind of interaction between a terminal group and the central metal ion has been observed by Fraser and Taube (32). As shown in Equation 52, the oxidation of a conjugated ligand at its furthest extremity from a metal ion may still involve participation by the electrons of the central metal ion by some conduction process. Participation of the central metal ion appears to be limited to reactions involving one-electron oxidants.



$$[(NH_3)_5Co{-}O\overset{O}{\overset{\|}{C}}{-}C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}H]^{+2} \xrightarrow[\text{or } H_2O_2]{Cl_2} [(NH_3)_5Co{-}O\overset{O}{\overset{\|}{C}}{-}C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}O]^{+}$$

$$[(NH_3)_5Co{-}O\overset{O}{\overset{\|}{C}}{-}C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}H]^{+2} \xrightarrow[MnO_4^-]{Co^{+3} \text{ or } S_2O_8^{-2}\,(Ag)^+} Co^{2+} + HO{-}\overset{O}{\overset{\|}{C}}{-}C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}OH$$

(52)

Template Hypothesis. A point to be emphasized is the particular steric advantage to be gained from the consideration of the several sites in the coordination sphere of a metal ion as constituting a template. These sites of known orientation may be utilized to hold reactive groups in proper position for sterically highly selective, multistep reactions. A first illustration of this phenomenon involves recent work showing that cis-oriented mercaptide groups react with difunctional active halogen compounds to form new chelate rings, without cleavage of the metal-donor atom bonds (72). This is outlined in Equation 53. This application of the chelate effect to ligand reactions should lead to the synthesis of macrocyclic ligands completely enclosing a planar metal ion. One can envision similar routes to the complete enclosing of octahedral metal ions in cagelike or clathrochelate ligands.

(53)

Conclusions

The development of the chemistry associated with the reactions of coordinated ligands may be expected to yield a number of broad contributions to chemistry. Such studies should lead to the acquisition of predictive control over large areas of known chemistry by providing a basis for the understanding of many catalytic and related phenomena. Many single observations on ligand reactions may provide the routes to new areas of chemistry. The elucidation of metal ion effects should provide the fundamental information necessary to a more thorough understanding of the action of metal ions in natural systems.

A number of topics have not been tendered the attention due them: enzyme processes, catalytic effects of metal ions in oxidation-reduction reactions, and the activation of small molecules such as H_2, O_2, and H_2O_2 by metal ions. This can be justified only by preoccupation with less well explored groups of reactions, which, it is to be hoped, will receive increased attention in future years.

Acknowledgment

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Literature Cited

(1) Akabori, S., Otani, T. T., Marshall, R., Winitz, M., Greenstein, J. P., *Arch. Biochem. Biophys.* **83,** 1 (1959).
(2) Arbuzov, A. E., Zoroastrova, V. M., *Doklady Akad. Nauk S.S.S.R.* **84,** 503 (1952).
(3) Barker, M. F., *Chem. News* **130,** 99 (1925).
(4) Basolo, F., Pearson, R. G., "Mechanisms of Inorganic Reactions," p. 158, Wiley, New York, 1958.
(5) *Ibid.,* p. 160.
(6) Bender, M. L., *Chem. Revs.* **60,** 53 (1960).
(7) Bender, M. L., Turnquest, B. W., *J. Am. Chem. Soc.* **79,** 1889 (1957).
(8) Bird, C. W., *Chem. Revs.* **62,** 283 (1962).
(9) Braye, E. H., Hoogzand, C., Hubel, W., Kruerke, U., Merenyi, R., Weiss, E., "Advances in the Chemistry of Coordination Compounds," S. Kirschner, ed., pp. 190 ff., Macmillan, New York, 1961.
(10) Brubaker, G., Busch, D. H., unpublished results.
(11) Busch, D. H., Bailar, J. C., Jr., *J. Am. Chem. Soc.* **78,** 1137 (1956).
(12) Busch, D. H., Burke, J. A., Jr., Jicha, D. C., Thompson, M. C., Morris, M. L., ADVAN. CHEM. SER., No. **37,** 125 (1963).
(13) Calvin, M., *Science* **130,** 1170 (1959).
(14) Chernyaev, I. I., *Ann. Inst. Platine* **7,** 52 (1929); *C.A.,* **24,** 2684 (1930).
(15) Coffield, T. H., Closson, R. D., Kozikowski, J., *J. Org. Chem.* **22,** 598 (1957).
(16) Collman, J. P., ADVAN. CHEM. SER., No. **37,** 78 (1963).
(17) Collman, J. P., Marshall, R. L., Young, W. L., III., Goldby, S. D., *Inorg. Chem.,* **1,** 704 (1962).
(18) Collman, J. P., Moss, R. A., Goldby, S. D., Trahanovsky, W. S., *Chem. and Ind.* (London) **1960,** 1213.
(19) Collman, J. P., Moss, R. A., Maltz, H., Heindel, C. C., *J. Am. Chem. Soc.* **83,** 531 (1961).
(20) Cossee, P., "Advances in the Chemistry of Coordination Compounds," S. Kirschner, ed., p. 241, Macmillan, New York, 1961.
(21) Djordjevic, C., Lewis, J. Nyholm, R. S., *Chem. and Ind.* (*London*) **1959,** 122.
(22) Dodge, R. P., Schomaker, V., *Nature* **186,** 798 (1960).
(23) Downs, R., Busch, D. H., unpublished results.

(24) Drinkard, W. C., Bauer, H. F., Bailar, J. C., Jr., *J. Am. Chem. Soc.* **82,** 2992 (1960).

(25) Drinkard, W. C., Huggins, D., Advan. Chem. Ser., No. **37,** 181 (1963).

(26) Eichhorn, G. L., Bailar, J. C., Jr., *J. Am. Chem. Soc.* **75,** 2905 (1953).

(27) Eichhorn, G. L., Marchand, M. D., *Ibid.,* **78,** 2688 (1956).

(28) Eichhorn, G. L., Trachtenberg, I. M., *Ibid.,* **76,** 5183 (1954).

(29) Ewens, R. V. G., Gibson, C. S., *J. Chem. Soc.* **1949,** 431.

(30) Figgins, P. E., Busch, D. H., *J. Am. Chem. Soc.* **82,** 820 (1960); *J. Phys. Chem.* **65,** 2236 (1961).

(31) Findley, W. R., Busch, D. H., unpublished results.

(32) Fraser, R. T. M., Taube, H., *J. Am. Chem. Soc.* **82,** 4152 (1960).

(33) Frend, M., *Ber.* **21,** 931 (1888).

(34) Gautier, M., *Ann. chim. phys.* **4** (17) 203 (1869).

(35) Geisenheimer, G., *Ibid.,* **6** (23) 231 (1891).

(36) Guillemard, H., *Bull. soc. chim. France* **4** (1) 270 (1907).

(37) Halpern, J., "Advances in Catalysis and Related Subjects," Vol. XI, p. 301, Academic Press, New York, 1959.

(38) Hartley, E. G. J., *J. Chem. Soc.* **97,** 1066 (1910); **101,** 705 (1912); **103,** 1195 (1913).

(39) Hartley, E. G. J., Powell, H. M., *Ibid.,* **1933,** 101.

(40) Heldt, W. Z., "Advances in the Chemistry of Coordination Compounds," S. Kirschner, ed., p. 321 ff, Macmillan, New York, 1961; Advan. Chem. Ser., No. **37,** 99 (1963).

(41) Hubel, W., Braye, E. H., *J. Inorg. Nucl. Chem.* **10,** 250 (1959).

(42) Ireland, R. E., Marshall, J. A., *J. Am. Chem. Soc.* **81,** 2907 (1959).

(43) Jicha, D. C., Busch, D. H., 135th Meeting ACS, Atlantic City, 1959.

(44) Kirch, L., Orchin, M., *J. Am. Chem. Soc.* **80,** 4428 (1960).

(45) Kluiber, R. W., *Ibid.,* **82,** 4839 (1960).

(46) Krause, R. A., Goldby, S. D., Advan. Chem. Ser., No. **37,** 143 (1963).

(47) Krause, R. A., Jicha, D. C., Busch, D. H., *J. Am. Chem. Soc.* **83,** 528 (1961).

(48) Kroll, H., *Ibid.,* **74,** 2036 (1952).

(49) Krumholtz, P., *Ibid.,* **75,** 2163 (1953).

(50) Kurtz, A. C., *J. Biol. Chem.* **122,** 477 (1937–8); **180,** 1253 (1949).

(51) Lindet, L., *Compt. rend.* **98,** 1382 (1884); **101,** 164 (1885).

(52) Longuet-Higgins, H. C., Orgel, L. E., *J. Chem. Soc.* **1956,** 1969.

(53) Malatesta, L., "Progress in Inorganic Chemistry," F. A. Cotton, ed., Vol. 1, Chap. 5, Interscience, New York, 1959.

(54) Martin, D. F., Advan. Chem. Ser., No. **37,** 192 (1963).

(55) Natta G., *J. Inorg. Nucl. Chem.* **8,** 589 (1958).

(56) Natta, G., Pasquon, I., "Advances in Catalysis and Related Subjects," Vol. XI, pp. 2 ff, Academic Press, New York, 1959.

(57) Nunez, L. J., Eichhorn, G. L., *J. Am. Chem. Soc.* **84,** 901 (1962).

(58) Orgel, L., "Introduction to Transition-Metal Chemistry. Ligand Field Theory," p. 139, Wiley, New York, 1960.

(59) Pauson, P. L., *Proc. Chem. Soc.* **1960,** 297.

(60) Pfeiffer, P., Offermann, W., Werner, H., unpublished manuscript.

(61) Pfeiffer, P., Offermann, W., Werner, H., *J. prakt. Chem.* **159,** 313 (1941).

(62) Powell, H. M., Bartindale, G. W. R., *J. Chem. Soc.* **1945,** 799.

(63) Rausch, M. D., Advan. Chem. Ser., No. **37,** 56 (1963).

(64) Reihlen, H., Illig, R., Wittig, R., *Ber.* **58,** 12 (1925).

(65) Sato, M., Okawa, K., Akabori, S., *Bull. Chem. Soc. Japan* **30,** 937 (1957).

(66) Schutzenberger, P., *Compt. Rend.* **70,** 1287, 1414 (1870); *Bull. Soc., Chim.* **2** (14) 97, 178 (1870).

(67) Schutzenberger, P., Fontain, *Ibid.,* **2** (17) 386, 482 (1872).

(68) Shimura, Y., *Bull. Chem. Soc. Japan* **31,** 311 (1958).

(69) Sternberg, H. W., Wender, I., Spec. Publ. No. 13, pp. 35 ff, Chemical Society, London, 1959.

(70) Stiles, M., Finkbeiner, H. L., *J. Am. Chem. Soc.* **81,** 505 (1959); Abstracts, 141st Meeting, ACS, Washington, D. C., March 1962.

(71) Strecher, W., Schurigan, M., *Ber.* **42,** 1767 (1909).

(72) Thompson, M. C., Busch, D. H., Burke, J. A., Jr., Jicha, D. C., Morris, M. L., Advan. Chem. Ser., No. **37,** 125 (1963); *Chem. Eng. News,* **40,** 57 (Sept. 17, 1962).

(73) Thompson, M. C., Busch, D. H., *J. Am. Chem. Soc.* **84,** 1762 (1962).

(74) Verter, H. S., Frost, A. E., *Ibid.,* **82,** 85 (1960).

(75) Watt, G. W., Sharif, L. E., Helvenston, E. P., *Inorg. Chem.* **1,** 6 (1962).

(76) Werner, Alfred, *Z. anorg. Chem.* **22,** 91 (1900); *Ann.* **351,** 65 (1907); **386,** 1 (1912).

(77) White, J. M., Manning, R. A., Li, N. C., *J. Am. Chem. Soc.* **78,** 2367 (1956).

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Metal Ion Catalysis of Nucleophilic Organic Reactions in Solution

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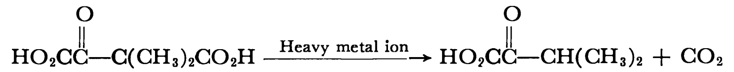
Catalysis by metal ions is a powerful method of accelerating organic reactions in solution. Metal ions have been shown to catalyze (or promote) a large number of organic reactions, including the hydrolysis of carboxylic acid esters, carboxylic acid amides, phosphate esters, phosphonate esters, halophosphates, pyrophosphates, and Schiff bases, carboxylation and decarboxylation reactions, the hydrogenation and hydration of unsaturated systems, olefin-forming elimination reactions, transaminations, aldol condensations, and nucleophilic displacement reactions. These metal ion–catalyzed reactions, the magnitude of the catalytic effects, the factors that determine the effectiveness of various metal ions, and the mechanisms by which metal ions function to accelerate reaction are surveyed.

Metal ions are known to catalyze many organic reactions in solution. Some examples of metal ion catalysis are discussed here and an attempt is made to point out the underlying principles concerning metal ion catalysis of organic reactions. Since the field is very large, it is necessary to limit discussion and to omit the topics of metal ion–catalyzed redox reactions and metal ion–catalyzed polymerization reactions, although the latter are extremely important.

Metal Ion Decarboxylation and Carboxylation Reactions

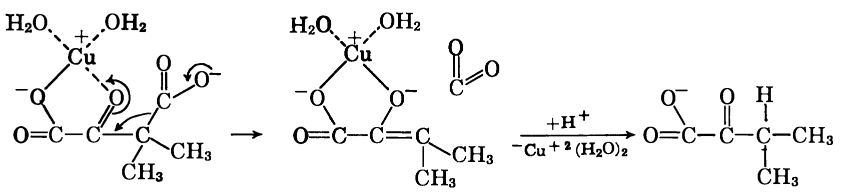
Although metal ions do not catalyze the decarboxylation of monocarboxylic acids in solution, a variety of metal ions catalyze the decarboxylation of oxaloacetic acid anion, leading to the formation of pyruvic acid (*27*). The metal ions involved were cupric, zinc, magnesium, aluminum, ferric, ferrous, manganous, and cadmium, approximately 10^{-2} to 10^{-3} *M* (*27*). Of these, the aluminum, ferric, ferrous, and cupric ions were the most efficient; sodium, potassium, and silver ions were inactive. This process involves the decarboxylation of a β-keto acid, which undergoes a relatively facile uncatalyzed decarboxylation. However, not every decarboxylation of a β-keto acid is catalyzed by metal ions—only those such as oxalosuccinic acid or oxalacetic acid, which contain a second carboxylic acid group directly adjacent to the ketonic function (*55*). In the aluminum ion–catalyzed decarboxylation of β-keto acids, an intermediate with an intense absorption in the region of 250 to 270 mμ was formed. It was presumed that this was the chelate of the enolate ion of the reactant with the metal ion and that this complex subsequently underwent decomposition to give the products. The monocarboxylic acid, acetoacetic acid, formed such a complex with aluminum ion, but this complex, in contrast to the oxaloacetic acid complex, was stable and did not decompose (*25*).

Steinberger and Westheimer (*56*) carried out an elegant analysis of the metal ion catalysis of the decarboxylation of dimethyloxaloacetic acid and some of its derivatives. The reaction utilized by them was



$$HO_2C\overset{\overset{O}{\|}}{C}—C(CH_3)_2CO_2H \xrightarrow{\text{Heavy metal ion}} HO_2C\overset{\overset{O}{\|}}{C}—CH(CH_3)_2 + CO_2$$

A highly absorbing enolic intermediate was identified spectroscopically in the region of 230 to 270 mμ. Since the reactant cannot enolize (because the molecule contains two methyl groups on the α-carbon atom), while the product can enolize, the enolic intermediate must be that corresponding to the product ketone. The effect of pH on the rate of the decarboxylation reaction shows that the metal ion complex of the dinegative ion is decarboxylated and not a complex of the singly charged anion or the undissociated acid. Thus various donor atoms in the substrate molecule are available for chelate formation. Since the monoester of dimethyloxaloacetic acid (in which the carboxylic acid group adjacent to the ketone is esterified) is not subject to metal ion catalysis while the diion is, the metal ion must be associated with the carboxylate ion gamma to the one which is lost. Copper, the metal ion most extensively investigated, is usually planar in coordination compounds; therefore the metal ion is probably not coordinated with the carbonyl oxygen and with both of the carboxylate ion groups. On this basis coordination of the metal ion to the gamma-carboxylate ion and the carbonyl group is postulated and it is postulated that the reaction sequence is:



Since aluminum ion is a strong catalyst, no valence change of the metal ion is involved in the reaction. The following observations of the decarboxylations catalyzed by ferric ion are strongly indicative of the above process.

Bright yellow → green → blue → deep blue → colorless
DMOAA + Fe^{+3} complex   Fe^{+3}-enolate complex   products

The above mechanism assigns an electrophilic function to the metal ion. During decarboxylation, an electron pair initially associated with the carboxylate ion group is transferred to the rest of the molecule. A metal ion, because of its positive charge, should assist this transfer (*46*).

A corollary of this argument is that the higher the charge and the more readily the metal coordinates with the carbonyl group, the greater should be the

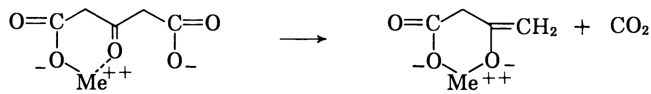
Table I. Effect of Metal Ions on Rate of Decarboxylation of Dimethyloxaloacetic Acid (55)

Metal Ion	*Concn.*	*pH*	*k, Min.*$^{-1}$
None	...	4.6	0.0024
Cu^{+2}	0.001	4.6	0.143
Al^{+3}	0.001	4.6	0.128
Ni^{+2}	0.01	4.6	0.0216
Mn^{+2}	0.01	4.6	0.0058
None	...	2.4[a]	0.0032
Fe^{+2}[b]	0.002	2.4[a]	0.0102
Fe^{+3}	0.002	2.3[a]	0.301
None	...	0	0.00032
Pd^{+2}	0.01	0	0.00061

[a] Solution unbuffered. [b] Experiment conducted under nitrogen.

catalytic activity of that ion. This general rule is amply borne out by Table I.

Prue (*48*) investigated the metal ion-catalyzed decarboxylation of the dianion of acetonedicarboxylic acid. He found that while the undissociated acid,



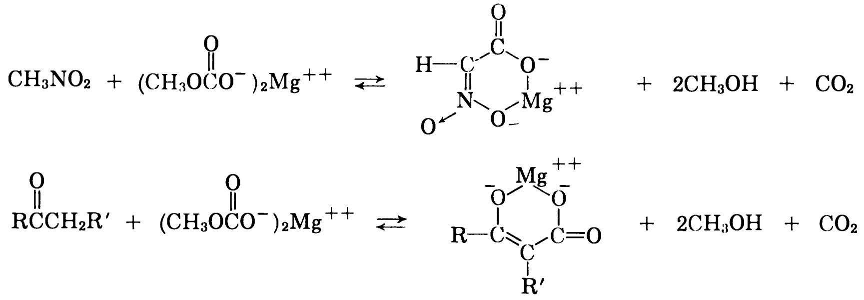
the singly charged anion, and the dinegative ion all decarboxylated at different rates, the dianion was most strongly influenced by metal ions.

A large number of bivalent and trivalent cations were utilized as catalysts in this reaction. The effectiveness of the cation as a catalyst strictly paralleled its power of forming a complex with the malonate ion, a model for the transition state of the reaction. This parallelism strikingly shows that the ability of a metal ion to catalyze this process depends on its ability to complex with the transition state.

The effect of various coordinating agents upon cupric ion catalysis of the dimethyloxalacetic acid and the acetonedicarboxylic acid decarboxylations are informative. Negative ions such as citrate and acetate diminish the catalytic activity of cupric ion; the amount of diminution is much greater for citrate than for acetate. In the decarboxylation of acetonedicarboxylic acid, it is calculated that while the $Cu^{+2}A^{-2}$ and $CuOAc^{+}A^{-2}$ species are catalytically active, the species $Cu(OAc)_2A^{-2}$ is completely inactive. These facts are in agreement with the assumption that any ligand that reduces the effective charge of the complex or reduces the concentration of the metal ion–substrate complex will reduce the catalytic effectiveness of the metal ion. On the other hand, a complex-forming agent which does not destroy the charge on the cupric ion does not destroy the catalytic activity. Thus pyridine, which readily forms complexes with cupric ion, promotes the decarboxylation of dimethyloxaloacetic acid. Thus in an enzymatic process involving a metal ion, the protein part of the enzyme may have two functions: the normal function of imparting specificity with respect to substrate, and complexing the metal ion in a way to enhance its activity.

Finally, the absence of catalysis by such highly charged ions as $Co(NH_3)_6^{+3}$ indicates that the cation catalysis noted here is due to an interaction of a specific short-range character–that is, a chelate–and not to a purely electrostatic interaction.

Metal ions will not catalyze the decarboxylation of monocarboxylic acids, presumably because metal ion complexation with the ground state is more stable than complexation with the transition state. A reversal of this argument indicates that metal ions might catalyze the carboxylation of substances containing so-called active hydrogen atoms, since the metal ion complex in the transition state should be more stable than in the ground state—that is, the metal ion complex of carbon dioxide, or in this case magnesium methyl carbonate. Both ketones and aliphatic nitro compounds may be carboxylated by this method, an elegant organic synthetic tool, as well as an interesting catalytic phenomenon (58,59).



Metal Ion–Catalyzed Hydrolysis of Esters, Amides, and Thiol Esters

Esters. The hydrolysis of a number of esters has been shown to be subject to catalysis by metal ions. Structurally these esters are similar; they contain a secondary functional group which can serve as a ligand for a metal ion.

In 1951 Kroll (28) discovered that heavy metal ions effectively catalyze the hydrolysis of amino acid esters. As with all amines, amino acid esters would be expected to form coordination compounds with heavy metal ions. The hydrolysis of amino acid esters complexed with cobaltous, cupric, manganous, calcium, and magnesium ions was extremely rapid, even at pH 7 to 8, where the amino acid ester itself is stable. When the amount of metal ion was varied, the rate constant of the hydrolysis varied, reaching a maximal value when the metal ion–ester ratio approached unity, indicating that the most active species was a complex of one metal ion and one ester molecule. The reaction was sensitive to pH, increasing fourfold from pH 7.5 to 8.5. This was interpreted as the participation of a hydroxyl ion in this reaction; however, the increase could also be attributed to the neutralization of the protonated amino acid ester (glycine ester has a pK_a of 7.75), resulting in a larger degree of complex formation. The latter explanation is to be preferred, on the basis that from pH 7.5 to 8.5 hydroxide concentration should increase tenfold, whereas the unprotonated glycine ester concentration should increase approximately threefold. The reaction is independent of buffer concentration and is thus not a general base-catalyzed reaction. Furthermore with the five metal ions utilized, the ester cleavage increased with the increasing tendency of the metal ion to enter into complex formation.

Table II. Effect of Several Metal Ions on Hydrolysis of Glycine Methyl Ester[a] (28)

Metal Ion	*pH*	$k_{obsd.}$, *Sec.*$^{-1}$
Cu^{+2}	7.3	0.0425
Co^{+2}	7.9	0.0156
Mn^{+2}	7.9	0.00351
Ca^{+2}	7.9	0.0007

[a] Temp. 25.4°; metal ion concn. 0.016 *M*; ester concn. 0.016 *M*.

The hydrolyses of glycine methyl ester and glycine ethyl ester appear to be nucleophilic processes, since as usual in nucleophilic reactions, the methyl ester reacts approximately twice as fast as the ethyl ester.

On the basis of this evidence it was postulated that a 1 to 1 complex is formed between the metal ion and the amino acid ester, in which the metal ion chelates with the amino group and the carbonyl oxygen of the ester, and that this chelate is attacked by hydroxide ion to give the'products of reaction through the intermediate formation of a tetrahedral addition compound.

With glycine ethyl ester and cysteine methyl ester in the presence of nickelous and cupric ions, a small increase in the (alkaline) bimolecular rate constant was shown to parallel an increase in the stability of the metal-ion complex (*65*).

Detailed kinetic studies revealed that glycine methyl ester and phenylalanine methyl ester in glycine buffer at pH 7.3 undergo a facile hydrolysis catalyzed by cupric ion (*11*). Under these conditions the reactions closely follow a first-order rate law in the substrate. Using these kinetic data it is possible to compare the rates of hydrolysis of DL-phenylalanine ethyl ester as catalyzed by hydronium, hydroxide, and cupric ion (see Table III).

Table III. Acidic, Basic, and Cupric Ion—Catalyzed Hydrolysis of DL-Phenylalanine Ethyl Ester at pH 7.3 and 25° C.

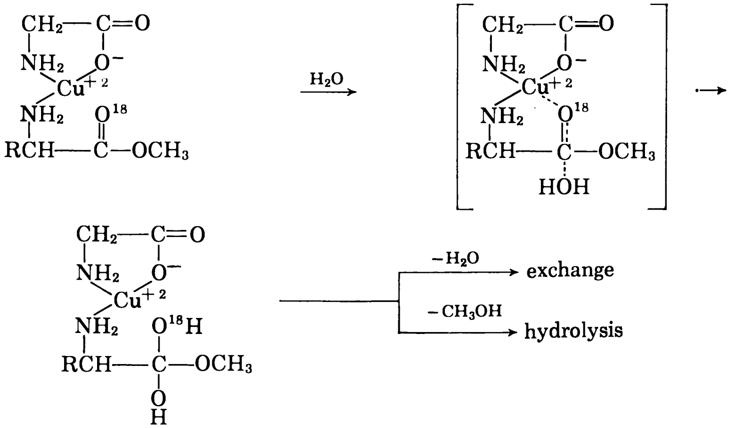
Catalyst	*Solvent*	k_2, *L./Mole Sec.*	k_1, *Sec.*$^{-1}$	*Reference*
H^+	70% dioxane		1.46×10^{-14} [a]	(*10*)
OH^-	85% ethanol	2.97×10^{-2}	5.8×10^{-9} [a]	(*10*)
Cu^+	Water		2.67×10^{-3} [b]	(*11*)

[a] The values of the hydrogen ion– and hydroxide ion–catalyzed reactions at pH 7 were extrapolated from the values at pH 1 and 13, respectively, assuming a change in the rate constant directly proportional to the change in the hydrogen (or hydroxide) ion concentration. This calculation must be viewed as an approximation, since the pH-rate profile of this reaction has not been determined. It may be predicted that the rate constant of the hydroxide ion–catalyzed reaction at pH 7 will be somewhat higher than that listed.

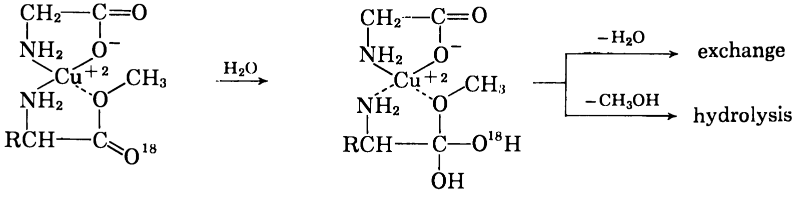
[b] The rate constant for the cupric ion catalysis equals k_3K [(glycine)Cu^+]. To obtain k_3, the true catalytic constant for cupric ion catalysis, approximations must be made for K and for [(glycine)Cu^+]. K, defined as (glycine-Cu^{+2}-ester) / (glycine-Cu^{+2}-ester), is assumed to be 10^3, on the basis of the stability constant of methyl glycinate with cupric ion reported to be 3.83 (log K) (*65*). A lower value is chosen, since the second stability constant is in general lower than the first, and the charge on the cupric ion in the latter complexation (+1) is less than that of the model system. The phenomena described above occur in the first and second complexations of cupric ion with glycine, where the second constant is about 1 to 1.5 pK units lower than the first. On the basis of this equilibrium constant and of the concentrations used in the experiment it can be straightforwardly calculated that K/(glycine-Cu^{+2}) is of the order of 1. Therefore the value in the table is a reasonable estimate of k_3, the catalytic constant of the cupric ion system.

The enhanced reactivity in the cupric ion–catalyzed hydrolysis cannot be due solely to the electrostatic effect of an attack of hydroxyl ion on a positively charged α-amino ester, since the introduction of a positive charge, two atoms from the carbonyl group of an ester, increases the rate constant of alkaline hydrolysis by a factor of 10^3 (*10*), whereas there is a difference of approximately 10^6 between the cupric ion–catalyzed and the alkaline hydrolyses of DL-phenylalanine ethyl ester. The effective charge on the cupric ion–glycine (buffer)–ester complex is +1, so that the factor of 10^6 cannot be explained by an increase in charge over that present in the case of betaine. Furthermore, the reaction cannot be due to attack by a water molecule on a positively charged α-amino acid ester, since the rate constant of the acidic hydrolysis of phenylalanine ethyl ester is very small. It thus seems reasonable to postulate that the rapid hydrolysis of α-amino esters at pH 7.3, as catalyzed by cupric ion, is due to a direct interaction of the metal ion with the reaction center, the ester group.

Carbonyl oxygen exchange was found during the cupric ion–catalyzed hydrolysis of DL-phenylalanine ethyl ester-*carbonyl*-O^{18} at pH 7.3 (*11*). This indicates that an additional intermediate is formed in this reaction. A mechanism (*11*) consistent with both the kinetic evidence and the oxygen-exchange evidence is given below.



Another possible explanation for the oxygen exchange results is a complexation of the cupric ion with the amino group and the methoxyl oxygen of the ester in the transition state of the reaction. This complex would unambiguously permit the formation of a tetrahedral addition intermediate in which the two oxygen atoms were equivalent and therefore capable of exchange. It is not possible to decide between these two possible pathways by which the cupric ion could catalyze this reaction, for both should lead to a facile reaction by polarization of the carbonyl carbon atom.



In the first mechanism the transition state would contain a partially negative carbonyl oxygen atom which could be stabilized to a greater extent electrostatically than the essentially neutral ether oxygen in the transition state of the second mechanism. On this basis the first mechanism is favored.

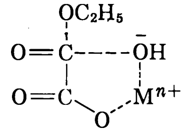
Catalysis by metal ions has also been demonstrated in the hydrolysis of esters containing an α- or β-carboxylate ion. The alkaline hydrolysis of potassium ethyl oxalate and potassium ethyl malonate is catalyzed by calcium, barium, hexaaminocobalt(III), and thallous ion, in that order (*22*). The oxalate ester is catalyzed to a greater extent than the malonate ester, which in turn is more susceptible to catalysis by metal ion than the corresponding adipate ester. Alkali metal ions, on the other hand, have only a small negative salt effect on the hydrolysis of potassium ethyl malonate.

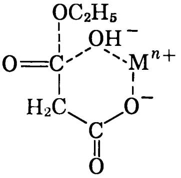
Table IV gives the relative catalytic reactivities of the various ions calculated on the basis that the undissociated ion given is the catalytic species.

Table IV. Metal Ion Catalysis of Hydrolysis of Esters Containing Free Carboxylate Ion (22)

	Ester		
Base	*EtOx*$^-$	*EtMal*$^-$	*EtAd*$^-$
OH^-	29.2	0.778	2.01
TlOH	1330	5.65	4.37
$BaOH^+$	9200	38.0	...
$CaOH^+$	...	39.8	7.94
$Co(NH_3)_6OH_2^+$	1740	16.0	17.1

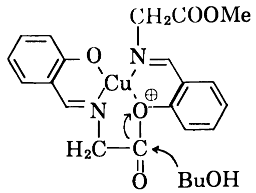
On the basis of the structural and metal ion effects, it is postulated that the transition states of the hydrolyses which are catalyzed by calcium, barium, cobaltic, and thallous ions can be represented by the chelate structures:





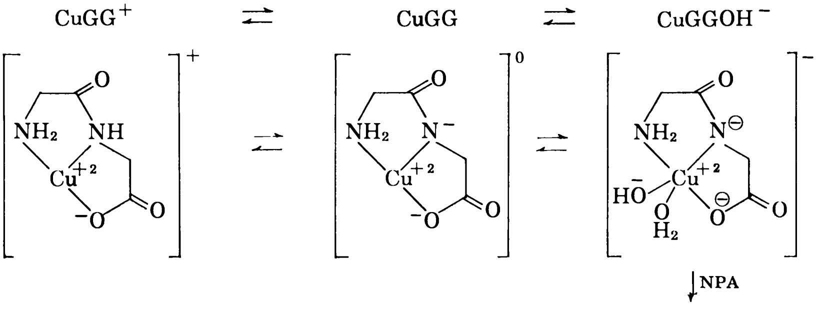
These chelates are structurally similar to that postulated above for the metal ion–catalyzed hydrolysis of α-amino esters; the position of the protons in the transition state is different, but this is a completely arbitrary distinction. A further distinction is that the metal ion is facilitating attack in this instance not by a polarization of the substrate molecule, but rather by the positioning and fixation of the hydroxide ion at the reaction site. It is not clear which of these two representations—for the amino acid esters involving polarization or for the carboxylate esters involving fixation of the hydroxide ion—is the correct interpretation. It is conceivable that both are correct. A similar explanation will account for the large effect of calcium ions on the alkaline hydrolysis of acetylcitric and benzoylcitric acids (*53*).

Facile transesterification and amidation reactions, closely related to the hydrolytic processes mentioned above, occur with bis-(salicylaldimine)-copper(II) chelates of α-amino acid esters. In these chelates the amino group of the ester is not coordinated directly with the copper ion, but is rather first transformed to an aldimine of salicylaldehyde, which would be expected to chelate well with a metal ion. The transesterification of the amino acid methyl ester in *n*-butyl alcohol yields the butyl ester after 10 minutes of refluxing. Likewise the butylamide is made by only 10 minutes of refluxing in *n*-butylamine. Two mechanisms have been proposed for this process. In one it is postulated that the cupric ion coordinates with the carbonyl oxygen atom, facilitating reaction by polarization of the carbonyl group, as described above; in the other, that the oxygen atom of the salicylaldimine attacks the carbonyl group, leading to the following intermediate:



which is attacked readily by the nucleophile, *n*-butyl alcohol or *n*-butylamine. The second possibility is preferred because the complex is known to have a square planar configuration and therefore the stereochemical preference would go to the intermediate described above (*61*).

Glycylglycine complexes with a number of heavy metal ions such as cupric, nickelous, manganous, cobaltous, zinc, and cadmium ions. These complexes involve the free α-amino group, the free carboxylate ion, and the peptide bond itself, leading to a bicyclic complex, such as $CuGG^+$. In two cases, complexes with cupric and nickelous ions, but apparently not with others (*16, 23, 24, 38, 42, 49*), it is possible for this complex to lose the peptide proton, leading to the neutral complex such as CuGG, and to associate with a hydroxide ion as shown in complex $CuGGOH^-$ (*23*).

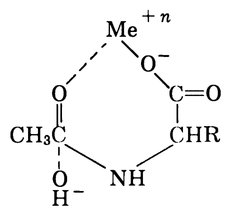


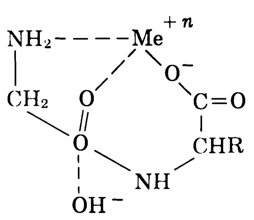
The catalysis of the hydrolysis of *p*-nitrophenyl acetate by complex $CuGGOH^-$ has been investigated (*23*). In weakly basic medium this species catalyzed the hydrolysis of *p*-nitrophenyl acetate. This catalysis took precedence over catalysis by free hydroxide ion because of the higher concentration of the former species in the relatively low pH region (7 to 10). However, the second-order catalytic rate constant for $CuGGOH^-$ is about one sixtieth of that of hydroxide ion, indicating that the inherent catalytic activity of a ligand hydroxide ion is less than that of free hydroxide ion, as one might expect from electrostatic considerations. The virtue of the metal ion complex thus lies in its ability to carry appreciable amount of hydroxide ion at a pH where very little free hydroxide ion could exist.

Amides. Metal ions catalyze the hydrolysis of a variety of amides, including acylamino acids, dipeptides and tripeptides, and amino acid amides. In all these compounds it is possible for a metal ion to complex with one or more ligand groups, either amine or carboxylate ion functions, in addition to the amide group. Thus the structural prerequisites for the metal ion catalysis of amide hydrolysis are the same as those for ester hydrolysis.

Metal ions have been shown to promote the hydrolysis of glycine amide and of phenylalanylglycine amide (*39*). Cupric ion, cobaltous ion, and nickelous ion, in that order, catalyze the hydrolysis of glycinamide in slightly alkaline solution (pH 9 to 10). In the absence of metal ions phenylalanylglycine undergoes ring closure to 3-benzyl-2,5-diketopiperazine; in the presence of cupric ion, however, at pH 5, hydrolysis of both the amide and peptide bonds is competitive with ring closure. The effect of catalysis by metal ions in the hydrolysis of amides is not nearly as striking as in the hydrolysis of esters—for example, the cupric ion-catalyzed hydrolysis of glycinamide is only about twentyfold greater than the spontaneous hydrolysis in the presence of $0.02M$ cupric ion. This result is surprising, since most of the infrared evidence for the interaction of metal ions and carboxylic acid derivatives has involved amides, and the amide group would be expected to be a better ligand for a metal ion than the ester group because of the greater basicity of the former.

Bamann and coworkers (*3*, *6*, *7*) have demonstrated catalysis of the hydrolysis of acylamino acids, dipeptides, and tripeptides with a variety of metal ions in slightly alkaline solution. They have investigated several dozen metal ions, most of which belong to the rare earth series. Those ions with the highest catalytic activity are cerium(IV) > cerium(III) > lanthanum(III). The reactions were carried out mainly at pH 8.6 and 70° in an ammonia–ammonium chloride buffer with a metal ion concentration equivalent to the substrate concentration. Under these conditions the metal ion exists almost exclusively in the form of a hydroxide gel. Under these conditions the hydrolysis of $0.0001M$ glycylleucine with cerium(IV) has a half life of 12 hours, while the reaction with cerium(III) has a half life of 36 hours and the reaction with lanthanum(III) has a half life of 10 days. Bamann postulates that the metal ion forms a chelate with the substrate, the amide group serving as one ligand, and that this complex is the kinetically reactive species. Certainly the effectiveness of the metal ion catalyst is connected with the magnitude of the positive charge of the ion. However, this factor is not the sole determining factor, and it is difficult to find a simple basis of correlating the activity of the several dozen metal ions that have been investigated.

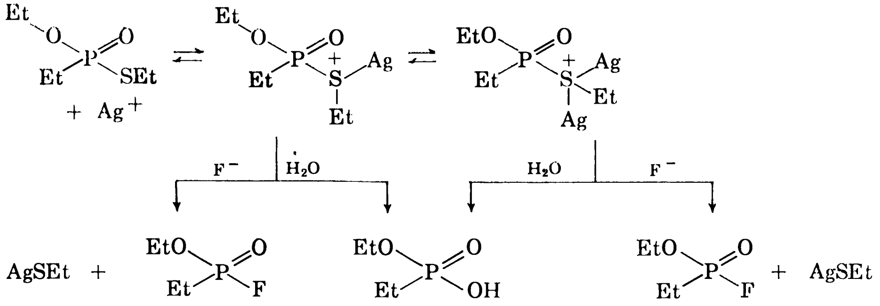




Thiol Esters. Thiol esters are particularly susceptible to cleavage by heavy metal ions such as mercuric, lead, or silver ion. This reaction was first noted in a nonaqueous system when an alcoholic mercuric acetate solution was treated with a thiol ester (*50*). Thiol esters such as acetyl coenzyme A (*37*), acetoacetyl coenzyme A (*57*), and thioaspirin (*9*) undergo hydrolysis in aqueous solution at neutrality almost instantaneously in the presence of stoichiometric amounts of mercuric ion salts. In each case a metal mercaptide is produced. In the hydrolysis of acetoacetyl-S-coenzyme A, a mercuric chelate involving two oxygen atoms of the acetoacetyl group and two oxygen atoms of the coenzyme A portion of the molecule was postulated as an intermediate (*57*). Since mercuric ion will cleave simple esters containing no secondary ligand groups, such chelation does not appear to be essential. Presumably the coordination of the sulfur atom with a mercuric ion is the principal driving force of this reaction.

Silver ion also catalyzes nucleophilic reactions of thiol esters, including reactions of acetylhomocysteine thiolactone (*12*) and diethylethylphosphonothiolate (*52*). In the first reaction, an insoluble complex of silver ion and the substrate was first produced at pH 7.5, which then reacted with the nucleophile, in this case an amino group of a protein. In the second reaction silver ion complexes of the substrate were also postulated, on the basis that silver ion complexes with sulfur are much more stable than those with oxygen (*1*). The complexes postulated were 1:1 and 2:1 silver ion–substrate complexes. These complexes were suggested to react with the nucleophiles, water and fluoride ion, giving as products phosphonic acid and phosphonyl fluoride, respectively, and silver mercaptide. It is evident that the last reaction at least must involve only the direct interaction of a silver ion with the sulfur atom of the thiol ester without chelate formation. Therefore it appears the metal ion–catalyzed reactions of thiol esters are unique, in that they involve complex formation, but not chelate formation in their catalytic mechanism.

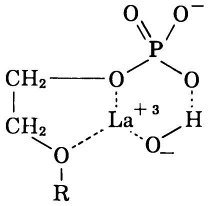
Rigorously most of the reactions described above should not be called metal ion–catalyzed reactions but rather metal ion–promoted reactions, since the metal ions are consumed stoichiometrically in most instances.

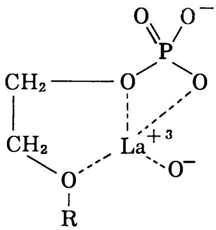


Metal Ion Catalysis of Phosphate Derivatives

Metal ions have been shown to catalyze the hydrolysis of phosphate esters, phosphoric and phosphonic acid halides, and various phosphoric acid anhydrides including acyl phosphates, pyrophosphate derivatives, and ATP.

The hydroxides of lanthanum, cerium, and thorium promote the hydrolysis of α-glyceryl phosphate in the region from pH 7 to 10. For example, at pH 8.5, lanthanum hydroxide (gel) accelerates the alkaline hydrolysis of α-glyceryl phosphate by more than a thousandfold. The rate of the metal ion–catalyzed reaction is considerably increased by a nitrogen- or oxygen-containing substituent in the β-position in the ester. It can therefore be suggested that the reaction proceeds through the complex as shown below, in which the lanthanum ion is coordinated with the β-substituent as well as with an oxyanion or an oxygen atom of the leaving group (*5*, *13*). Since dilution of the lanthanum hydroxide gel with water increases the rate of the reaction, it is the metal ion in solution (in equilibrium with the gel) and not the metal ion of the gel which is catalytically active. 1-Methoxy-2-propylphosphate is hydrolyzed by lanthanum hydroxide gel at pH 8.5 with complete retention of stereochemical configuration and cleavage of the P—O bond.

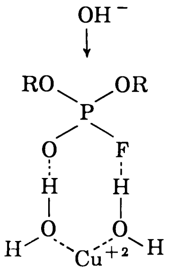


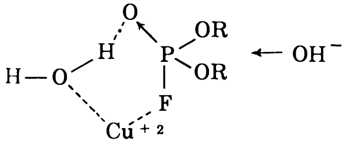


A determination of the pH dependence of the lanthanum hydroxide gel-promoted hydrolysis of β-glyceryl phosphate revealed that the two maxima exist in the pH-rate profile, one at pH 8.6 which presumably involves the species $La(OH)^{+2}$ and another (smaller) maximum at pH 10.4 which involves the species $La(OH)_2^+$ (*4*). Presumably the same kind of catalytic mechanism is operative in both cases. These reactions may serve as models for the metal ion–promoted alkaline phosphatases which have been shown to proceed with P—O cleavage (and with no oxygen exchange).

In addition to the hydrolysis of monoesters of phosphoric acid, the hydrolysis of diesters of phosphoric acid is also susceptible to metal ion catalysis, in particular by multivalent cations such as barium, stannous, and cupric ions. The diesters which undergo metal ion–catalyzed hydrolyses include open-chain diesters and cyclic diesters containing both five- and six-membered rings (*54*).

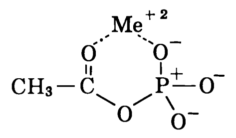
The hydrolysis of diisopropylphosphorofluoridate and of isopropylmethylphosphonylfluoridate is also susceptible to metal ion catalysis (*14, 19, 62*). In the hydrolysis of the former compound (DFP), by cupric ion, the magnitude of the metal ion catalysis was affected by the complexing agents of the cupric ion. Maximum activity is limited to complexes in which firmly bound ligands (other than aquo groups) do not completely fill the first coordination sphere of the cupric ion. Furthermore, free cupric ion is by far the best catalyst, as opposed to its chelated derivatives. Suggestions for the catalytic action of cupric ion are:





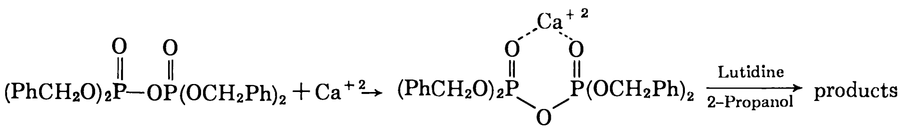
In the hydrolysis of the latter compound, Sarin, catalysis by cerous, cupric, and manganous ions in the form of bifunctional species which have a nucleophilic center (hydroxide ion) and an electrophilic center (M^+) was particularly effective (*19*). Although the hydroxometallic ions are considerably weaker bases than hydroxide ion itself, they are catalytically more active by a factor of 10. This activity can be explained by the bifunctionality of these compounds mentioned above.

The nucleophilic reactions of acetyl phosphate are catalyzed by cations such as magnesium (*26*), calcium (*15, 32*), and even lithium (*30*). Most of the reactions involve catalysis of hydrolysis. Calcium ion catalyzes a neutral as well as a base-catalyzed hydrolysis and also catalyzes the attack of glycine and of mercaptoacetate on the carbonyl group. At pH 7.7 magnesium ion catalyzes the hydrolysis of acetyl phosphate markedly and the catalyzed reaction is first order in magnesium ion as well as in acetyl phosphate. The catalysis by metal ion is greater at pH 7.7, where acetyl phosphate exists as a dinegative ion, than at pH 0.63, where it exists as a neutral molecule. It was therefore postulated that the following chelate may be formed in the metal ion–catalyzed reaction (*26*):

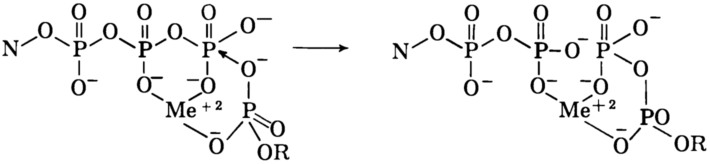


It is likely that the function of the metal ion is to facilitate reaction of the acyl group with water, hydroxide ion, mercaptide ion, or glycine by decreasing electrostatic repulsion by neutralization of negative charge as in the chelate above, and by aiding the expulsion of the phosphate group through general acid catalysis (*15*).

The solvolysis of tetrabenzyl pyrophosphate catalyzed by lutidine (see above) is further catalyzed a thousandfold by calcium ions. In the presence of 0.02*M* calcium ion and 0.2*M* lutidine, the solvolysis of tetrabenzyl pyrophosphate (with cleavage of the P—O bond) is increased by a factor of the order of 1,000,000 over the uncatalyzed reaction (*63*). The bivalent cation chelates with two oxygen atoms of the pyrophosphate ester, and the positive charge in the chelate greatly enhances the susceptibility of the phosphorus atom toward nucleophilic attack.



The enzymatic reactions of adenosine triphosphate (ATP), in which this compound acts as a phosphorylating agent, require magnesium ion. Although the metal ion in these reactions may act primarily as a bond between the nucleotide and the enzyme, a number of results, including those presented above, suggest that part of the enzymatic activity may be associated with a positive charge induced in a pyrophosphate group of the nucleotide by the bivalent cation. This effect is noted in the nonenzymatic hydrolysis of ATP in the presence of various divalent metal ions such as calcium, manganous, cupric, and cadmium (*31*, *59*). At pH 9 the rate of hydrolysis is accelerated tenfold by calcium ion, and at pH 5 sixtyfold by cupric ion. Presumably the position of complexing of the metal ion with ATP determines the position of cleavage of the substrate. Selective complexing of metal ions with ATP could then determine the cleavage at either the terminal or the internal phosphate groups of ATP, as found in enzymatic reactions. In addition to catalysis of hydrolytic reactions, divalent metal ions, including calcium, cadmium, and manganous ions, catalyze the nonenzymatic transphosphorylation of ATP with phosphate ions and carboxylate ions (*33*, *34*). The former reaction shows a sharp pH optimum at about 9. With manganous ions, the rate of the transphosphorylation reaction is optimum at a ratio of ATP to Mn^{+2} of 0.6 to 1.0, with inhibition at higher ratios. This nonenzymatic process, although proceeding more slowly than the enzymatic reaction, may serve as a model for enzymatic transphosphorylations utilizing ATP. It is suggested that the nonenzymatic (metal ion–catalyzed) reaction proceeds as follows and that the enzymatic phosphorylation reaction proceeds in an analogous fashion enhanced by suitable bonding of both the substrate and the metal ion to the enzyme surface. The essential point of this mechanism is that the metal ion, Me^{+2}, may coordinate with both the substrate and the (polydentate) nucleophilic agent; thus, it gathers and holds together the two species needed for this bimolecular reaction. This nonenzymatic transphosphorylation reaction is stimulated by alkali metal ions. There is still an absolute requirement for the bivalent metal ion, but alkali metal ions, in particular potassium ion, accelerate the reaction. Presumably this acceleration occurs by either an ion pair formation with ATP or a specific chelate formation of the alkali metal ion with ATP (or the transition state) (*35*).

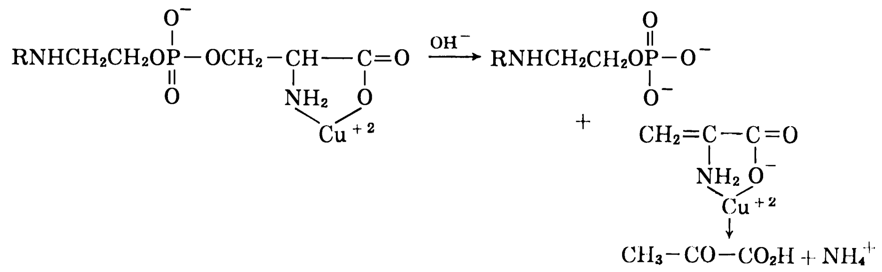


A corresponding reaction of acetate ion with ATP is also catalyzed by a bivalent metal ion. The reaction probably results in the formation of an acyl phosphate, which has not been identified as such but has been identified by trapping of the product with hydroxylamine. The best catalyst is beryllium ion, which catalyzes optimally at molar ratios of 1 to 1 or less. Acetate ion is presumably the reactive species, since the pH optimum of the reaction is 5. It is concluded from the pH effects in this study and in the transphosphorylation reaction that a complex of the metal ion and nucleophile must occur. Since acetate ion is a monodentate ligand, the mechanism postulated for the phosphorylation reaction above cannot be completely applicable to this case (*36*).

Those reactions of carboxylic acid and phosphoric acid derivatives which are susceptible to metal ion catalysis in nonenzymatic systems are almost without exception catalyzed by enzymes containing metal ions. This circumstantial evidence indicates strongly that the metal ions in the enzymatic reactions are concerned with the catalytic action, and not simply binding.

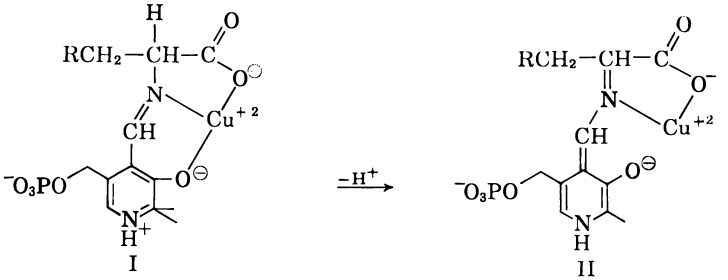
Metal Ion Catalysis of Substitution, Elimination, and Condensation Reactions

In any reaction where the cleavage of a carbon-hydrogen bond is important, the introduction of a metal ion into the molecule in the proper position will facilitate reaction. For example, in the elimination of the elements of a phosphoric acid monoester from the molecule below, the electrostatic attraction of the cupric ion facilitates removal of the proton on the α-carbon atom with subsequent elimination of the phosphoryl residue (*8*).



Another reaction in which the cleavage of a carbon-hydrogen bond is important is the bromination of ketones. In the bromination of ethyl acetoacetate and 2-carboethoxycyclopentanone, it was shown that multivalent cations are catalysts. In the latter reaction, cupric, nickelous, lanthanum, zinc, plumbous, manganous, cadmium, magnesium, and calcium ions were effective (*45*). One can interpret the effect of the metal ion in terms of its catalysis of the proton transfer from the ester to a base, whether the reaction is carried out in dilute hydrochloric acid solution (acid-catalyzed bromination) or in acetate buffer (base-catalyzed bromination).

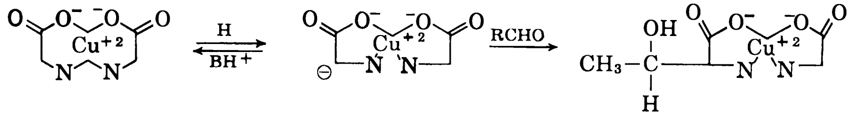
In a number of nonenzymatic reactions catalyzed by pyridoxal, a metal ion complex is formed—a combination of a multivalent metal ion such as cupric or aluminum ion with the Schiff base formed from the combination of an amino acid and pyridoxal (I). The electrostatic effect of the metal ion, as well as the "electron sink" of the pyridinium ion, facilitates the removal of an α-hydrogen atom to form the tautomeric Schiff base, II. Schiff base II is capable of a number of reactions characteristic of pyridoxal systems. Since the former asymmetric center of the amino acid has lost its asymmetry, donation of a proton to that center followed by hydrolytic cleavage of the system will result in a racemic amino acid. On the other hand, donation of a proton to the benzylic carbon atom followed by hydrolytic cleavage of the system will result in a transamination reaction—that is, the amino acid will be converted to a keto acid and pyridoxal will be converted to pyridoxamine. Decarboxylation of the original amino acid can occur instead of the initial loss of a proton. In either case, a pair of electrons must be absorbed by the pyridoxal system, and in each case, the electrostatic effect of the metal ion facilitates this electron movement, as well as the subsequent hydrolytic cleavage (*40, 43*).



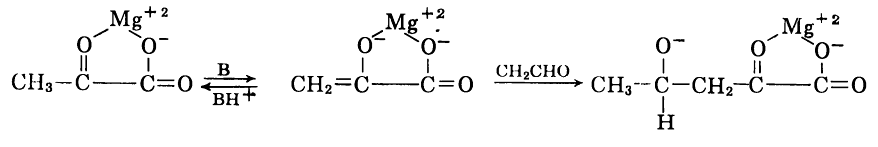
I

II

Related to the metal ion–pyridoxal reactions are a group of aldol condensation reactions catalyzed by multivalent metal ions. Copper glycinate is a stable metal ion complex in which two glycinate ions complex with cupric ion. In basic solution, this complex will condense either with formaldehyde to produce the copper complex of serine or with acetaldehyde to produce copper complexes of threonine and allothreonine (*2, 51*). These reactions do not occur at pH 7 but occur readily at pH 11 at 100°. Presumably catalytic activity of the metal ion in these systems is due to the polarization of the carbon-hydrogen bond, facilitating the formation of an enolate ion. It has been reported that the effectiveness of the metal ion can be markedly improved by use of the cobalt(III) complex of bis(ethylenediamine), which combines with only one molecule of glycine, leading to a complex with an over-all charge of +2, instead of zero as above (*41*).



In general, any molecule capable of producing an enolate ion and also possessing two ligands for chelation of a metal ion will exhibit such a catalysis. For example, it has been reported (*47*) that magnesium ion catalyzes the aldol condensation of pyruvate with acetaldehyde, presumably through a mechanism such as:



The catalysis of the cleavage of carbon-halogen bonds by complexation with metal ions such as silver or mercuric ion is a well-known phenomenon. The compounds susceptible to this action are alkyl halides capable of forming carbonium ions. The complexed anions such as in mercuric nitrate, mercuric perchlorate, or hydrated mercuric ion do not exhibit a simple relationship between their effect on the total rate and on the relative distribution of products stemming from water or the anion. This evidence is indicative of the following catalytic mechanism:

$$RX + Me^+ \rightarrow R^+ + MeX$$

$$R^+ + H_2O \rightarrow \text{products}$$

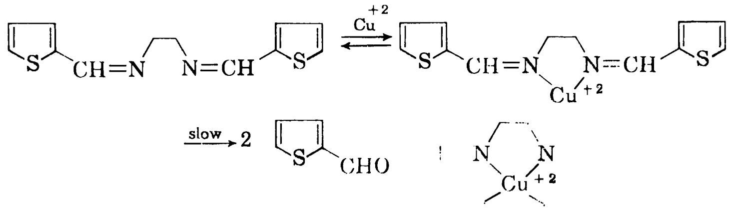
Silver and mercuric ions are relatively specific in their action on alkyl halides. The explanation of this fact is, of course, the great affinity of these metal ions for halide ion as evidenced by the small ionization of mercuric halides, the insolubility of silver halides, and the fact that the silver halides dissolve in excess halide ion to form complexes of the type AgX_2^- (*21*).

In the displacement of bromide ion by thiosulfate ion in the S_N2 reaction

$$^-S_2O_3^{-2} + BrCH_2CO_2^- \rightarrow {}^-O_3S_2CH_2CO_2^- + Br^-$$

the rate of the reaction is accelerated by the addition of lanthanum chloride. This specific accelerating effect of lanthanum chloride may be explained most easily as a specific interaction of the metal ion and the negatively charged substrate, leading to an ion pair which is more susceptible from an electrostatic viewpoint to attack by thiosulfate anion than the original anion (*29*). Thus both S_N1 and S_N2 reactions are susceptible to metal ion catalysis.

The hydrolysis of certain Schiff bases is catalyzed by divalent metal ions such as cupric or nickelous ion. Spectrophotometric evidence indicates the formation of a metal ion complex of the substrate with subsequent facile cleavage of the complex.



It is postulated that the facile cleavage of the complex is due to the polarization of the carbon-nitrogen double bond. At pH 7, where these investigations were carried out, the spontaneous decomposition of the Schiff base is very slow, while the metal ion–catalyzed reaction has a half life of a few minutes. Since the hydrolysis of Schiff bases is catalyzed by hydrogen ion, the metal ion catalyst can be postulated to be a superacid catalyst present in neutral solution (*17*, *18*).

Conclusions

Whereas the term "metal ion catalysis" has been continually used, the more rigorous term in many instances should be "metal ion promotion," since often the metal ion is consumed stoichiometrically in the reaction.

The metal ion can be considered a superacid that may exist in neutral solution (*64*). Its most important characteristic as catalyst or promoter is its positive charge. In many reactions variation in catalytic action can be directly correlated with variation in the magnitude of the cationic charge. Since this charge is the effective charge of the metal ion complex, and not the metal ion alone, the electrostatic nature of the ligands attached to the metal ion is equally important to the inherent charge of the metal ion. In a number of instances, metal ion catalysis of a polyvalent metal ion has been reduced to nil by complexation of the metal ion with anionic ligands. Furthermore, charge density may be more important than net charge. The electrostatic force of a charge on another charge or on a dipole can be calculated from simple theory to depend on the inverse second or third to fifth power of the distance, respectively. With this restriction on the field of the metal ion, it is necessary for maximal effect to introduce the metal ion directly into the substrate molecule to be catalyzed. On this basis the effectiveness of a metal ion should increase with the decreasing ionic radius of the ion. However, with transition-metal ions, the electrostatic effect of the ion also is affected by the shielding of the ligand from the nuclear charge of the metal ion by the *d* electrons (*44*).

All polar organic reactions are influenced by electronic changes within the molecule. It is the principal function of a metal ion catalyst to bring about such changes, probably to a greater extent than any other chemical species. The simplest example of such an effect is the fact that the acidity of a water molecule coordinated with a cupric ion (a hydrated cupric ion) is 10^7 times greater than that of a free water molecule. Therefore the acidity of an organic substrate complexed with cupric ion might also be 10^7 times greater than that of the organic substrate alone (*44*). This means that a considerable shift of electron density occurs on coordination of a metal ion with an organic substrate and therefore reactions which depend on an electron movement can probably be effectively facilitated by a metal ion, whether this electron movement results in the cleavage of a carbon-carbon, carbon-hydrogen, carbon-oxygen, carbon-sulfur, or carbon-halogen bond.

Many reactions require the presence of an "electron sink" in the molecule to absorb electron density produced by a reaction. The introduction of a suitably positioned metal ion in a substrate undergoing such a reaction will facilitate such a reaction. Other reactions require the neutralization of a negative charge, to reduce electrostatic repulsion during reaction. A metal ion will also serve this purpose. Still other reactions require the polarization of a particular bond to effect reaction. Again, the introduction of a metal ion in a specific position in the substrate molecule will accelerate the reaction. Finally the stabilization of leaving groups will often facilitate reaction. When the leaving groups are halide or mercaptide ions, metal ions can facilitate such reactions.

Both a proton and a metal ion can introduce a positive charge into a substrate molecule and effect the electronic changes listed above. A metal ion, however, is superior to a proton on several grounds. A metal ion can introduce a multiple positive charge into an organic molecule, whereas a proton can introduce only a single positive charge. Furthermore, a metal ion can operate in neutral solution, whereas a proton cannot. Finally, a metal ion can coordinate several donor atoms, whereas a proton can coordinate with only one donor atom.

In listing the ways in which metal ions may promote organic reactions, the requirement that the metal ion be suitably positioned within the substrate molecule was emphasized. Specific complexation or chelation of the metal ion with the substrate appears to be an absolute requirement of metal ion catalysis. In many cases chelation appears to be the rule, which usually means that the substrate must contain a donor atom in addition to the reactive center of the molecule with which the metal ion also complexes, or must contain two donor atoms in addition to the reactive center. Many attempts have been made to correlate the effectiveness of catalysis by a series of metal ions with the relative formation constants of the complexes. Such correlations have been successful in a number of reactions, but unsuccessful in others. In the successful correlations the complex chosen for the correlation closely approximates the transition state of the reaction. This indicates that the metal ion complex must stabilize the transition state of the reaction in order to assist the reaction effectively, and that metal ion complex formation in the ground state can have an effect exactly opposite to that of catalysis, since in such a case the ground state becomes stabilized.

Since coordination compounds of metal ions may contain a large number of ligands, it is possible to form not only a metal ion complex with the substrate but also a metal ion complex with both the substrate and the nucleophilic agent. Thus the metal ion can serve as a central collection point for both components of a bimolecular reaction, and presumably assist the reaction by making the entropy of activation more positive. Further, such a complex of metal ion, substrate, and nucleophile will be more susceptible to reaction when both the substrate and nucleophile contain negative charges, for in the complex, electrostatic repulsion between these two species will be decreased. The most efficient complex of metal ion, substrate, and nucleophile that can be envisioned is one in which both the substrate and the nucleophile are attached to the metal ion at positions other than those at which eventual covalent interaction will take place. Furthermore, such a complex must have suitable stereochemistry for the covalent interaction between the two ligands to occur. A metal ion complex containing hydroxide ion as a ligand can serve as a carrier of hydroxide ion in neutral solution, just as the metal ion itself can be considered to approximate a superproton in neutral solution. Furthermore, a metal ion complex containing hydroxide ion (or another nucleophile) can be considered to be a bifunctional catalyst, the metal ion serving as a general acid, and the hydroxide ion serving as a general base or nucleophile.

A metal ion may also assist reaction by stabilization of a reactive intermediate. It is conceivable in this instance that the metal ion does not interact with the ground state, but, by the stabilization of an intermediate in the reaction sequence, promotes the over-all reaction.

Literature Cited

(1) Ahrland, S., Chatt, J., Davies, N. R., *Quart. Rev.* **12**, 265 (1958).
(2) Akabori, S., Otani, T. T., Marshall, R., Winitz, M., Greenstein, J. P., *Arch. Biochem. Biophys.* **83**, 1 (1959).

(3) Bamann, E., Haas, J. G., Trapmann, H., *Arch. Pharm.* **294,** 569 (1961).
(4) Bamann, E., Mutterlein, W. D., *Chem. Ber.* **91,** 471 (1958).
(5) Bamann, E., Nowotny, E., *Ber.* **81,** 451, 455, 463 (1948).
(6) Bamann, E., Rother, A., Trapmann, H., *Naturwissenschaften* **43,** 326 (1956).
(7) Bamann, E., Trapmann, H., Rother, A., *Chem. Ber.* **91,** 1744 (1958).
(8) Beatty, I. M., Magreth, D. I., *J. Am. Chem. Soc.*, **82,** 4986 (1960).
(9) Bender, M. L., Schonbaum, G. R., unpublished observations.
(10) Bender, M. L., Turnquest, B. W., *J. Am. Chem. Soc.* **77,** 4271 (1955).
(11) *Ibid.*, **79,** 1889 (1957).
(12) Benesch, R., Benesch, R. E., *Proc. Natl. Acad. Sci. U. S.* 44, 848 (1958).
(13) Butcher, W. W., Westheimer, F. H., *J. Am. Chem. Soc.* **77,** 2420 (1955).
(14) Courtney, R. C., *et al.*, *Ibid.*, **79,** 3030 (1957).
(15) Di Sabato, G., Jencks, W. P., *Ibid.*, **83,** 4393 (1961).
(16) Dobbie, H., Kermack, W. O., *Biochem., J.* **59,** 246, 257 (1955).
(17) Eichhorn, G. L., Bailar, J. C., Jr., *J. Am. Chem. Soc.* **75,** 2905 (1953).
(18) Eichhorn, G. L., Trachtenberg, I. M., *Ibid.*, **76,** 5183 (1954).
(19) Epstein, J., Rosenblatt, D. H., *Ibid.*, **80,** 3596 (1958).
(20) Halpern, J., James, B. R., Kemp, A. L. W., *Ibid.*, **83,** 4097 (1961).
(21) Hammett, L. P., "Physical Organic Chemistry," p. 138, McGraw-Hill, New York, 1940.
(22) Hoppé, J. I., Prue, J. E., *J. Chem. Soc.* **1957,** 1775.
(23) Koltun, W. L., Fried, M., Gurd, F. R. N., *J. Am. Chem. Soc.* **82,** 233 (1960).
(24) Koltun, W. L., Gurd, F. R. N., *Ibid.*, **81,** 301 (1959).
(25) Kornberg, A., Ochoa, S., Mehler, A. H., *J. Biol Chem.* **174,** 159 (1947).
(26) Koshland, D. E., Jr., *J. Am. Chem. Soc.* 74, 2286 (1952).
(27) Krebs, H. A., *Biochem. J.* **36,** 303 (1942).
(28) Kroll, H., *J. Am. Chem. Soc.* **74,** 2036 (1952).
(29) Kunnap, H., Pats, A., *Apophoreta Tartuensis* **1949,** 377; *Chem. Abs.* **44,** 7629 (1950).
(30) Kurz, J. L., Gutsche, C. D., *J. Am. Chem. Soc.*, **82,** 2175 (1960).
(31) Lipkin, D., Markham, R., Cook, W. H., *Ibid.*, **81,** 6075 (1959).
(32) Lipmann, F., Tuttle, L. C., *J. Biol. Chem.* **153,** 571 (1944).
(33) Lowenstein, J. M., *Biochim. Biophys. Acta* **28,** 206 (1958).
(34) Lowenstein, J. M., *Biochem. J.* **70,** 222 (1958).
(35) *Ibid.*, **75,** 269 (1960).
(36) Lowenstein, J. M., Schatz, M. N., *J. Biol. Chem.* **236,** 305 (1961).
(37) Lynen, F., Reichert, E., Rueff, L., *Ann.* **574,** 14, 31 (1951).
(38) Martin, R. B., Chamberlin, M., Edsall, J. T., *J. Am. Chem. Soc.*, **82,** 495 (1960).
(39) Meriwether, L., Westheimer, F. H., *Ibid.*, **78,** 5119 (1956).
(40) Metzler, D. E., Ikawa M., Snell, E. E., *Ibid.*, **76,** 648 (1954).
(41) Murakami, M., Takahashi, K., *Bull. Chem. Soc. Japan* **32,** 308 (1959).
(42) Murphy, C. B., Martell, A. E., *J. Biol. Chem.* **226,** 37 (1957).
(43) Nunez, L. J., Eichhorn, G. L., *J. Am. Chem. Soc.*, 84, 901 (1962).
(44) Orgel, L. E., *Biochem. Soc. Symp.* **15,** 8 (1958).
(45) Pedersen, K. J., *Acta Chem. Scand.* **2,** 252 (1948).
(46) *Ibid.*, pp. 252, 385.
(47) Pricer, quoted by Horecker, B. L., *J. Cell. Comp. Physiol.* **54,** Supp. 1, 95 (1959).
(48) Prue, J. E., *J. Chem. Soc.* **1952,** 2331.
(49) Rabin, B. R., *Biochem. Soc. Symp.* **15,** 21 (1958).
(50) Sachs, G., *Ber.* **54,** 1849 (1921).
(51) Sato, M., Okawa, K., Akabori, S., *Bull. Chem. Soc. Japan* **30,** 937 (1957).
(52) Saville, B., *J. Chem. Soc.* **1961,** 4624.
(53) Smith, A., Olin, B., *Z. physik. Chem.* **177,** 131 (1936).
(54) Smith, F., Drummond, G. I., Khorana, H. G., *J. Am. Chem. Soc.* **83,** 698 (1961).
(55) Speck, J. F., *J. Biol. Chem.* **178,** 315 (1948).
(56) Steinberger, R., Westheimer, F. H., *J. Am. Chem. Soc.* **73,** 429 (1951).
(57) Stern, J. R., *J. Biol. Chem.* **221,** 33 (1956).
(58) Stiles, M., *J. Am. Chem. Soc.* **81,** 2598 (1959).
(59) Stiles, M., Finkheimer, H. L., *Ibid.*, **81,** 505 (1959).
(60) Tetas, M., Lowenstein, J. M., Abstracts 141st Meeting, ACS, 1962, p. 47C.
(61) Verter, H. S., Frost, A. E., *J. Am. Chem. Soc.* **82,** 85 (1960).
(62) Wagner-Jaureeg, T., Hackley, B. E., Jr., Lies, T. A., Owens O. O., Proper, R., *Ibid.*, **77,** 922 (1955).
(63) Westheimer, F. H., *Spec. Publ. Chem. Soc.*, No. **8,** 1 (1957).
(64) Westheimer, F. H., *Trans. N. Y. Acad. Sci.* **18,** 15 (1955).
(65) White, J. M., Manning, R. A., Li, N. C., *J. Am. Chem. Soc.* **78,** 2367 (1956).

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Metal Ion Catalysis in Biological Systems

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The participation of metal ions in biological reactions is illustrative of many ways in which metal ions bring about ligand reactions. Generally such participation involves the effect of the metal's positive charge in drawing electrons away from the reactive bond in the organic molecule. The aconitase reaction demonstrates the importance of the stereochemistry of the metal in holding the reacting molecules in positions favorable for reaction. The involvement of vitamin B_{12} in biological reactions is thought to exemplify the catalysis of electron transfer. Metal ions are associated with biological macromolecules such as proteins and nucleic acids and control the activity of these substances by influencing their three-dimensional structures. Metal-complexing reactions are involved even in the impregnation of bacteria by phage virus.

Of all the properties of metal ions that make them useful in the catalysis of biological reactions, the most important is also the simplest; metal ions constitute a concentration of positive charge. As a consequence of this positive charge they are capable of holding two molecules together by interaction with points of negative charge or with negative dipoles on these molecules. The molecules may be stabilized in combination with metals, or they may be weakened to the extent that they are disrupted. Most of the instances in which metal ions activate enzymes are manifestations of the latter phenomenon—i.e., the ability of metal ions to labilize covalent bonds.

The other metal ion characteristics that are familiar to the inorganic chemist, such as their stereochemistry, their electronic configuration, and their oxidation reduction potential, are also very useful in biological phenomena. In fact, perhaps the major difference between the inorganic chemist and the biochemist in their view of metal ion catalysis is that the inorganic chemist produces the metal complexes that he studies, whereas the biochemist analyzes metal complexes that are naturally occurring.

Biochemical reactions involve small organic molecules of a size to which the inorganic coordination chemist is accustomed, and they also involve molecules with molecular weights in the millions. Metal ions can mediate reactions between two small molecules. Such processes are simple inorganic processes, and need not be further discussed. They may bind a small molecule to a large one, as in the reaction of an enzyme with its substrate. Or they may establish connection between two giant biological macromolecules. Finally, as was discovered several years ago by Kozloff and his collaborators, metal ions can even serve a vital role in the attack of one biological entity upon another.

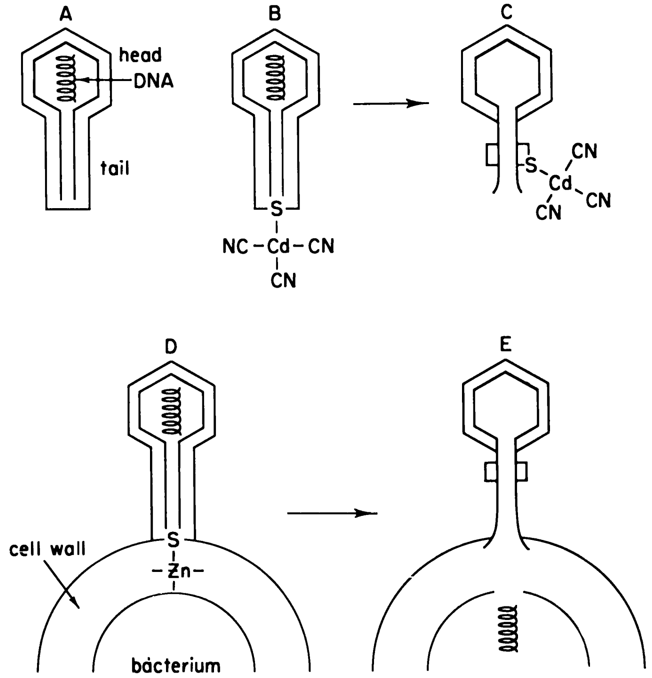


Figure 1. Viral invasion of bacterial cell (27)

A. Intact virus
B. Complex formation
C. Alteration of virus and contraction of tail sheath
D. Attachment of virus to bacterial cell wall
E. Injection of DNA into cell

Invasion of Bacteria by Virus

T_2 bacteriophage is a virus that can infect cells of the bacterium *E. coli*. The phage consists of a head in the form of a hexagonal prism to which a cylindrical tail of smaller diameter is attached (8) (Figure 1,*A*). The surface of both head and tail is made of protein. The head encloses molecules of deoxyribonucleic acid (DNA), which contain the coded information for the replication of the virus. (The virus itself has no machinery for self-replication, but when its DNA is injected into a bacterial cell, the bacterium begins to make virus according to the specifications of the phage DNA.) The tail contains a passage through which the

DNA must travel in order to infect a bacterial cell. The virus attaches itself to the bacterial cell by the tail and then injects the DNA into the bacterium (*27*).

The tail of the virus can be altered so that the sheath contracts and the DNA passageway becomes exposed. Several chemical and physical techniques are available for this alteration; all of the chemical methods involve reagents that break sulfur bonds (*27*). Among the reagents that behave in this manner are complexes of zinc, cadmium, and mercury, in which the ligands do not completely satisfy the coordination positions of the metals (*29*). Thus complexes of (ethylenedinitrilo)tetraacetic acid are inactive, whereas unsaturated cyanide complexes are most effective. Studies with varying concentrations of cadmium and cyanide indicate that the most active species is probably $Cd(CN)_3$ (*29*). The opening of the tail is apparently accomplished by the attachment of a metal complex to a sulfur bond at the tip of the tail through an unoccupied coordination position on the metal (Figure 1,*B*), and followed by the rupture of the sulfur bond (Figure 1,*C*).

Studies with the bacteria have shown that the bacterial cell wall contains a metal complex that can accomplish in the attached virus what the cadmium cyanide accomplishes in the unattached virus. The cell wall of *E. coli* contains zinc, which can be extracted with acid (*28*). When an intact phage particle attaches itself to a zinc-containing bacterial cell wall, the latter is broken down. When the zinc is removed from the bacterial cell wall, the phage loses its ability to digest it. However, phage particles with altered tails can break down the cell wall, even though its zinc has been removed. Finally, when zinc is re-added to bacterial cell walls that had been acid-extracted, the walls are again susceptible to attack by the intact virus (*28*). It is thus apparent that a zinc complex in the cell wall of the bacterium binds to a sulfur-containing bond in the phage (Figure 1,*D*), cleaving the latter, and releasing through the tail an enzyme that splits the wall of the bacterium, so that DNA can pass from the phage to the bacteria (Figure 1,*E*).

Metalloenzymes

The mechanism by which a metal ion is able to cleave a bond at the tip of the tail of the bacteriophage is presumably similar to a general mechanism that accounts for the activity of many metalloenzymes. The metal is the active site of the enzyme, having some of its coordination sites occupied by ligands on the enzyme, and some by ligands on the substrate molecule (Figure 2). The attach-

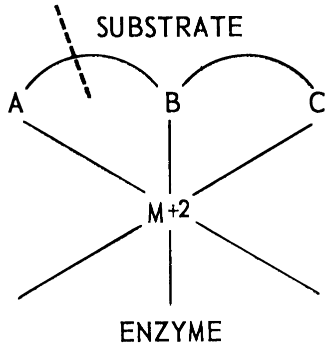
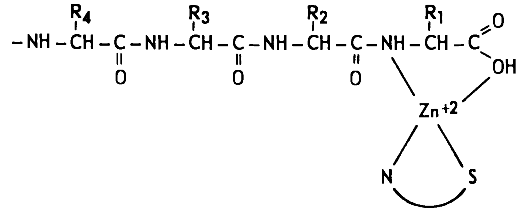


Figure 2. Metal-enzyme-substrate complex

ment of the metal to the substrate brings about a generalized drift of electrons in the direction of the metal. If the substrate contains a relatively weak bond—e.g., between ligands A and B—the electron drift toward the metal weakens such a bond even further and makes it more vulnerable to attack. Many hydrolytic enzymatic reactions may be explained in this fashion.

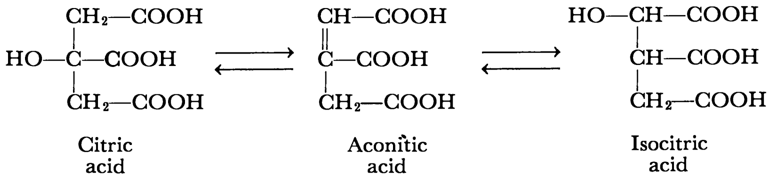
One of these is the action of carboxypeptidase (*40*), which cleaves the peptide linkage at the carboxyl end of a protein or polypeptide. The metal can



CARBOXYPEPTIDASE

chelate with the carboxyl group and the adjacent peptide linkage, thus drawing electrons toward itself and away from the protein, and especially from the hydrolysis-susceptible peptide bond (*40*). (The exact nature of the binding to the peptide linkage is undetermined; probably coordination occurs with loss of protons.) Recently, Vallee and his collaborators (*45*) have shown that carboxypeptidase does have one atom of zinc bound to each molecule of the enzyme, and they have obtained some good evidence about the nature of this binding. Zinc was removed (*11*) from the enzyme, by treatment with *o*-phenanthroline, producing apocarboxypeptidase, which is not active. The activity could be restored by the re-addition of zinc, or by the addition of Mn^{+2}, Co^{+2}, Fe^{+2}, or Ni^{+2} to the demetallized enzyme. The importance of the metal was thus demonstrated. It was possible to combine a second atom of zinc with the enzyme molecule, but without any enhancement of the activity, thus demonstrating the requirement of one, but only one, atom of the metal. The stability constants of the complexes of carboxypeptidase with Mn^{+2}, Co^{+2}, Ni^{+2}, Cu^{+2}, Zn^{+2}, Cd^{+2}, and Hg^{+2} were compared with the constants of the same metals with ethylenediamine (N-N chelation), glycine (N-O chelation), and 2-mercaptoethylamine (N-S chelation), leading to the conclusion that the metals were chelated to carboxypeptidase by sulfur and nitrogen ligands (*11, 46*).

A somewhat different type of reaction is catalyzed by the iron(II)-containing (*12*) enzyme aconitase, which brings about the interconversion of citric, isocitric, and aconitic acids by hydration and dehydration.



Evidence has been obtained by Speyer and Dickman (*43*) that this reaction proceeds through a common intermediate resonating carbonium ion structure, which is coordinated to iron in such a manner that the iron is always bound to the same ligands, regardless of the direction in which the reaction is proceeding (Figure 3).

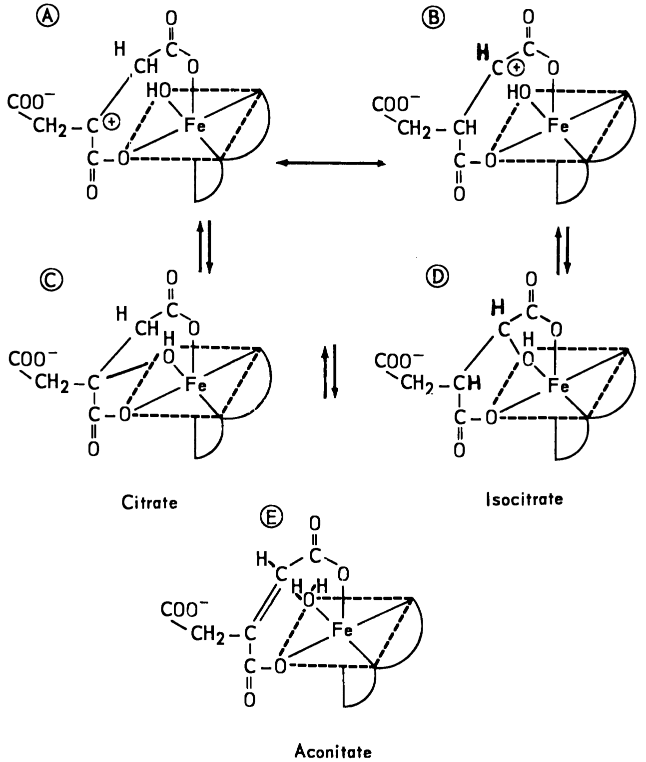
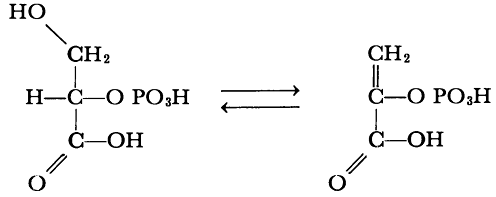


Figure 3. Mechanism of aconitase reaction (43)

If this mechanism is correct, the aconitase reaction is an excellent illustration of the influence of the stereochemistry of the metal, as well as its charge, upon the course of a biochemical reaction. The charge on the iron is, of course, responsible for the formation of the resonating carbonium ions A and B from C, D, or E. In C and D the flow of electrons toward iron severs the bond between carbon and the hydroxyl group, whereas in E the proton is released from coordinated water and attached to one of the two ethylenic carbon atoms. The stereochemistry of the iron atom can be credited with holding the organic molecule and the hydroxide in their proper spatial relationship in A and B. It has been recently demonstrated that the complexes of the aconitase substrates with nickel have the structures postulated by Speyer and Dickman and shown in Figure 3 (*19*).

Another enzyme with a function very similar to that of aconitase is enolase, which contains magnesium ion (*48*) and catalyzes the interconversion of phosphoglyceric acid and phosphoenolpyruvic acid. The magnesium can be replaced by



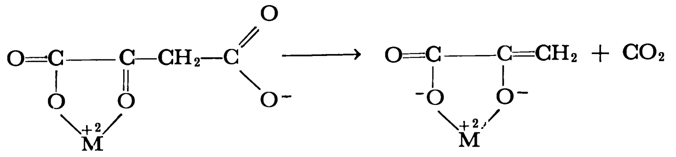
$$\begin{array}{c} HO \\ \diagdown \\ CH_2 \\ | \\ H-C-O\;PO_3H \\ | \\ C-OH \\ /\!/ \\ O \end{array} \;\rightleftarrows\; \begin{array}{c} CH_2 \\ \| \\ C-O\;PO_3H \\ | \\ C-OH \\ /\!/ \\ O \end{array}$$

Zn^{+2}, Mn^{+2}, Fe^{+2}, Cd^{+2}, Co^{+2}, and Ni^{+2}, although diminished activity results (*35*, *53*). Fundamentally the enolase and aconitase reactions are closely related, since the net result of both is the addition or subtraction of a molecule of water. In spite of this similarity, the metal ions associated with these two reactions are very different. It is one of the puzzling aspects of metalloenzyme chemistry that every enzyme has a different metal ion specificity. Each of these enzymes is associated in its natural state with a specific metal ion, which differs from enzyme to enzyme. It is possible to remove the naturally occurring metal from many of these enzymes and to reactivate them by the addition of other metals, as has been shown in the case of carboxypeptidase. The order in which the various metal ions fall in their ability to activate the different enzymes again varies from enzyme to enzyme.

At the outset it is difficult to comprehend this variability, if, as we have postulated, the effect of the charge on the metal ion in distorting the electrons of the substrate is of paramount importance to the function of the metal. It would then be expected that the stronger the bonds between the metal and the substrate, the greater will be the pull on the electrons and therefore the greater the catalytic effect. The order of activating ability of the metals should therefore be the same as the order of complex stability. Such an order is indeed frequently followed in nonenzymatic catalysis (*21*, *52*). Why, then, is enzymatic catalysis so relatively unpredictable in comparison with nonenzymatic catalysis?

One of the reasons for the lack of correlation of metal complex stability with enzyme-activating ability is probably that an enzyme must be specific for its substrate. Metal ions are nonspecific, and those metals which coordinate most strongly would tend to react with many substances in addition to the enzyme substrate. Furthermore, the most strongly coordinating metal ions would react with sites on the enzyme other than the reactive site and would therefore denature the enzyme. Finally, the strongest binding metals would remain bound to the product of the reaction, whereas the completion of the catalysis requires that the catalyst must be freed from the product in order again to become available for further catalytic activity (*16*). The metal of choice in the enzymatic reaction must therefore compromise the capacity to perform the desired function with a low tendency to engage in undesirable side reactions.

To elucidate the difference between the enzymatic and nonenzymatic participation of metal ions, it is clearly desirable to be able to compare the effect of a large number of metal ions upon the same reaction both in the presence and absence of the enzyme. For such a study to be feasible it is necessary to work with a metal-activated enzymatic reaction, which will also take place when the metal, but not the enzyme, is omitted. Such a reaction is the decarboxylation of oxaloacetic acid. The mechanism of metal catalysis of this reaction is similar to that assumed for carboxypeptidase, and can be represented as follows (*44*).



Fortunately, data have been collected by Speck (*41*) on the activity of a large number of metals in the enzymatic as well as the nonenzymatic reaction.

Equally auspicious is the fact that these data cover a wide range of metal ion concentrations, in the absence of which the comparison would have been much less effective.

The most remarkable feature that can be gleaned from the examination of Figure 4 is that the order of metal activation of the nonenzymatic reaction follows generally the order of complex stability, as Williams has pointed out (52). This is particularly true at low metal ion concentration—e.g., 10^{-3} M—where the metals in the first transition series, for example, are active in the order $Mn^{+2}<Fe^{+2}<Co^{+2}<Ni^{+2}<Cu^{+2}>Zn^{+2}$, the well-known Irving-Williams (25) order of complex stability. The other metals also fall in line.

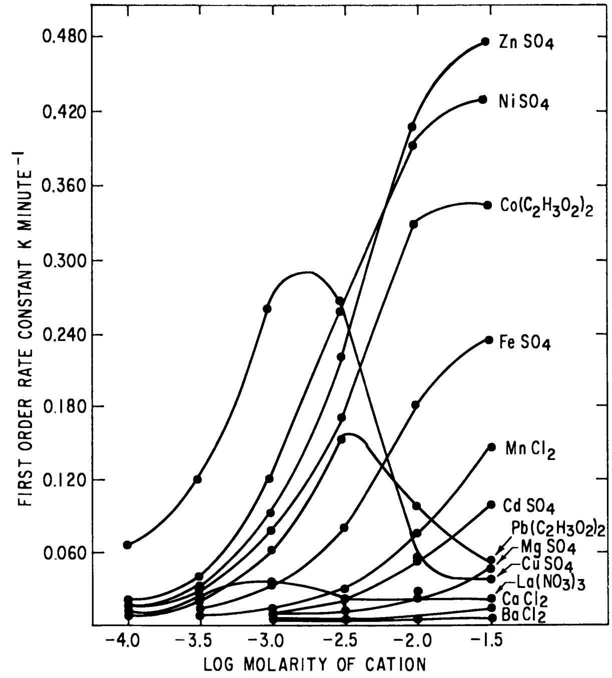


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Figure 4. Effect of metal ions on nonenzymatic decarboxylation of oxalacetic acid (41)

Several other features in this figure are worth noting. At the highest metal ion concentration, $10^{-1.5}M$, Cu^{+2}, which had been most active at $10^{-3}M$, becomes one of the poorest catalysts, since the activity curve for Cu^{+2} passes through an optimum at $10^{-2.8}M$. Pb^{+2} and La^{+3} are the only other metal ions that produce such an optimum within the concentration range that is available. However, at $10^{-1.5}M$, the strongest activating metals—i.e., Zn^{+2}, Ni^{+2}, Co^{+2}, and Fe^{+2}—form a plateau, indicating that they too could have reached optimal activity at a somewhat higher concentration. The weakest activating metals are just beginning to rise at maximum concentration. Such behavior can be explained if it is assumed that the reaction is catalyzed by all of the metals, when they are bound to the oxaloacetate as shown in the equation, in the order of the Irving-Williams sequence. The strongest coordinating metals, however, may occupy a second site on the oxaloacetate and the second reaction may be inhibitory. The order of inhibition on the second site would be expected to be the same as the order of activation on the first site. The strongest coordinating metals therefore begin to inhibit at low concentrations, and the shapes of the curves in Figure 4 are explained. [Some of these data were analyzed in a somewhat similar manner by Williams (52).]

The rates of the enzymatic reaction (Figure 5) are in general much greater than those of the nonenzymatic reaction. More important to the present discussion, Figure 5 reveals that optimum activity occurs at lower concentrations than in the nonenzymatic reaction. Moreover, unlike their behavior in the nonenzymatic activation, practically all of the metals pass through a peak within this concentration range. The most strongly coordinating metal, Cu^{+2}, is already on the decline at the lowest concentration studied, and has completely lost its activity at $10^{-3}M$. One of the weakest metals, Ca^{+2}, has already attained a plateau at the maximum concentration.

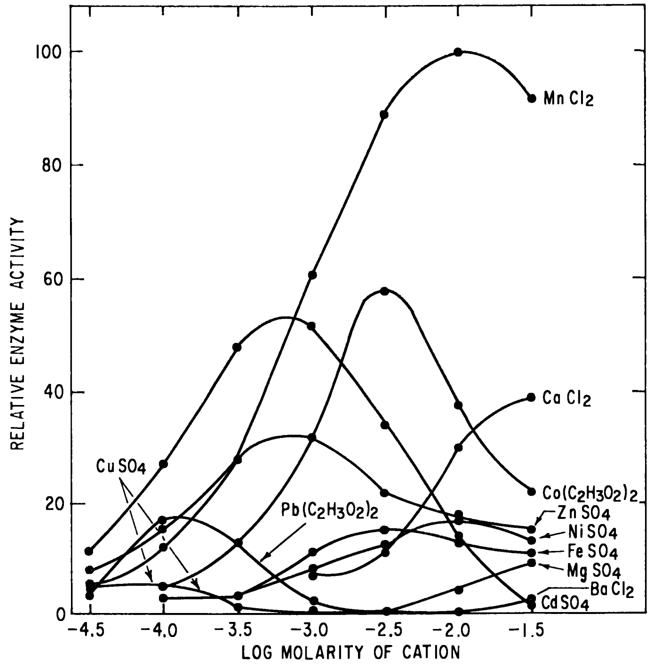

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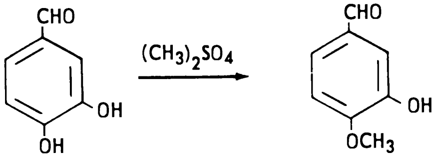
Figure 5. Effect of metal ions on enzymatic decarboxylation of oxalacetic acid (41)

If one examines the relative activating ability of the series of metals at given concentrations, it is possible to find many different orders, depending upon which concentration is selected. This circumstance is the consequence of the many intersections of the curves. Since enzymatic activation is generally measured at only one concentration of metal ions, the different orders of activation that have been observed can be partly explained on this basis. The most significant feature of Figure 5 is that there is a correlation with complex stability, if the metals are placed in the order of concentrations at which maximal activity is observed. This order follows the order of complex stability in general, although there are some discrepancies in the first transition series. It appears, therefore, that qualitatively the metals behave in the enzymatic reaction in a manner like that in the nonenzymatic reaction. Activation presumably occurs in the same way as in the nonenzymatic reaction. Inhibition probably involves attachment to a second site on the enzyme, rather than on the substrate.

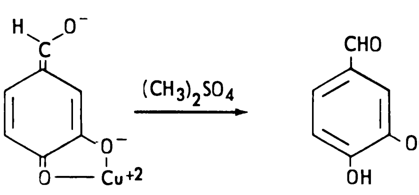
It may be concluded that both metal activation and metal inhibition follow the order of complex stability in enzymatic as well as nonenzymatic processes, and that this order cannot be observed at any one metal concentration when activation and inhibition occur simultaneously. However, the order is approximated by the sequence of peaks in a plot of activity *vs.* metal ion concentration.

Such a generalization is useful in that it provides clues to the nature of the participation of metal ions in a reaction, when the order of catalytic effect of the various metals is known. As a first example of such an approach, let us consider the case in which the order of inhibition correlates with the order of complex stability; such an order is frequently observed—e.g., urease (*39*). It may be concluded, in such an instance, that the metals do not activate the reaction, but inhibit it only. As a second example, if metal ions activate a reaction, but they do so in inverse order from that of complex stability, it follows that inhibition competes effectively with activation. Such an order is observed with enolase ($Mg^{+2} > Zn^{+2} > Mn^{+2} > Fe^{+2} > Co^{+2} > Ni^{+2}$) (*35*, *53*); presumably the inhibitory effect of the more strongly binding metals is responsible for the selection of the less active Mg^{+2} in the natural enzyme. Probably such effects are not as important in aconitase, making it possible for a stronger chelating metal to activate that enzyme.

Recently, Senoh, Tokuyama, and Witkop (*37*) have studied a metal-activated enzymatic reaction in the presence and the absence of enzyme, and have discovered that the order of effectiveness of the metals is exactly the reverse in the enzymatic and nonenzymatic processes. The reaction was *O*-methylation of 3,4-dihydroxybenzaldehyde. In the absence of divalent metal ions, the nonenzymatic reaction yields very predominantly the paramethylated product in neutral solution, since the *p*-hydroxyl group is the more electronegative. Metal complex formation



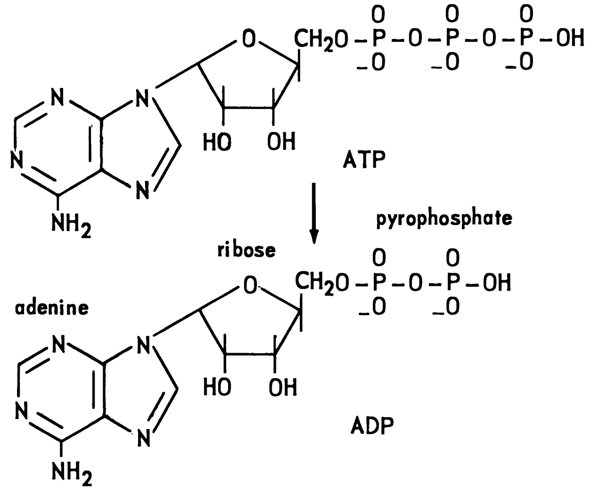
brings about an increase in production of the meta isomer, by favoring the formation of the phenoxide ion at the meta position:



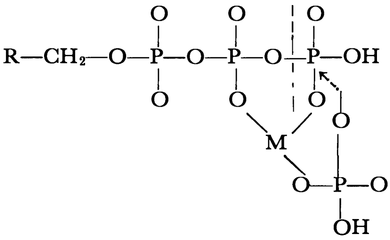
Cu^{+2} is by far the most effective in promoting meta-substitution, the order of effectiveness being $Cu^{+2} > Fe^{+2} > Ni^{+2} > Co^{+2} > Mn^{+2} > Zn^{+2} > Mg^{+2}$. This is the expected order, from complex stabilities, with the exception of the anomalous position of Fe^{+2}. In the enzymatic reaction, the order of effectiveness of the metal ions, in terms of total yield of methylated products, was the exact reverse, and it can be postulated that an inhibitory process is therefore of prime importance in the enzymatic reaction.

The studies on the methylation of dihydroxybenzaldehyde and the earlier studies on the decarboxylation of oxaloacetic acid illustrate a hypothesis about metal-catalyzed enzymes that is not proved but has been substantiated in a number of instances in which it has been tried. The hypothesis is that, if a metal constitutes the active site of an enzyme, it should be possible to carry out the reaction with metal ions alone in the absence of the enzyme. The rates of nonenzymatic reactions may be much lower, and the metal ions may be more active metal ions than those that activate the enzyme, for the reasons already discussed. This hypothesis is the basis for much of the work on metal catalytic reactions that are "models" for enzyme systems.

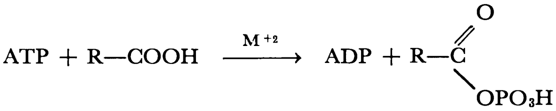
Perhaps one of the most important reactions of biochemistry is the cleavage of adenosine triphosphate (ATP) itno adenosine diphosphate (ADP). This reaction provides the necessary energy for a large number of processes, some of them individual intracellular reactions and others intercellular phenomena such as muscular contraction. The enzymatic cleavage of the terminal phosphate of ATP always requires a metal ion (usually magnesium or manganese), and recently Lowenstein has been able to carry out "model" experiments to show that metal ions can mediate such a cleavage unaided.



Lowenstein reacted ATP with orthophosphate (33) in the presence of metal ions, and obtained ADP and pyrophosphate as products. The most active metals in this reaction were, rather surprisingly for a nonenzymatic reaction, the alkaline earths, Cd^{+2} and Mn^{+2}; the members of the first transition series exhibited low activity. The reactive intermediate was formulated as follows:



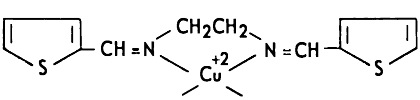
The enzymatic reaction was postulated to involve the same intermediate, with some of the coordinate bonds of the metal also attached to ligands on the enzyme. It was also possible, in the nonenzymatic reaction, to substitute an organic acid, such as acetate (*34*) for the orthophosphate; the reaction proceeded in like fashion to produce a phosphate ester:



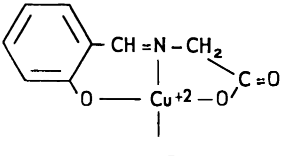
$$\text{ATP} + \text{R—COOH} \xrightarrow{\text{M}^{+2}} \text{ADP} + \text{R—C}(=\text{O})\text{OPO}_3\text{H}$$

The metal ion specificity for the reaction with acetate was different from that in the reaction with phosphate; in the former beryllium was most active, followed by nickel. The alkaline earths that were so effective with phosphate did not catalyze the reaction with acetate at all. The difference in metal specificity in the two reactions was explained by assuming that complexation with the orthophosphate and acetate constitutes an important function in the reaction.

The peculiar metal ion specificity of the ATP cleavage reaction may perhaps be explained by reference to some studies on the metal complexes of Schiff bases, which have provided clues to many aspects of biological metal catalysis. It was shown that metal ions will split the carbon-nitrogen double bond in thiophenaldehyde-ethylenediamine (*18*, *21*) as a consequence of the electronic-drift-to-metal phenomenon that has been discussed, but that metal ions actually stabilize the double bond in the salicylaldehyde-glycine Schiff base (*20*). The difference in



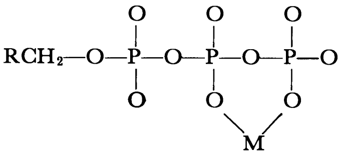
A



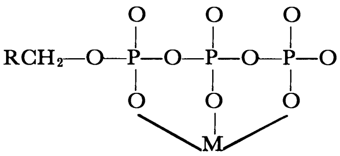
B

the effect of metal ions on A and B is interpreted by the fact that, even though the electronic shifts that occur in A should also take place in B, the cleavage of the double bond in A leaves all of the coordination positions to the metal intact, whereas the removal of salicylaldehyde from B would convert a very stable bicyclic chelate into a much less stable monocyclic chelate.

Returning to the ATP cleavage reaction, it may be supposed that some metal ions, probably the weakest complexers, form a monocyclic chelate by attaching to the terminal pyrophosphate only (C), whereas others, probably the strongest complexers, form a bicyclic chelate by binding the α-phosphate as well (D). By



C

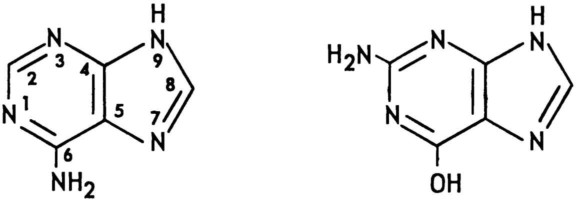


D

analogy with the Schiff base reactions, metal complex formation in C would result in bond labilization, whereas in D it would actually strengthen the ATP molecule. In this manner it is possible to rationalize the superior activity of the weak metals in this reaction. Recent nuclear magnetic resonance studies on the metal complexes of ATP lend some support to the hypothesis that mono- and bicyclic chelates may be formed with ATP and different metals (*10*).

Metal Ions and Nucleic Acids

If the terminal pyrophosphate is removed from a molecule of ATP, the remainder is AMP, adenosine monophosphate, one of the four building blocks of the important biological macromolecules, the nucleic acids. There are two types of nucleic acids (*26*): ribonucleic acid (RNA), and deoxyribonucleic acid (DNA). RNA is a polymer of four different "nucleotides," one of which is AMP, the ribose phosphate of adenine. The other three nucleotides are also ribose phosphates of heterocyclic "bases," guanine, cytosine, and uracil. The structure of the four bases is shown in Figure 6.



Adenine **Guanine**

Cytosine **Uracil**

Figure 6. Structures of nucleotide bases

RNA contains a "backbone" ribose phosphate polymeric chain, with one of the four heterocyclic bases attached to each ribose; a segment of the RNA molecule might look as in Figure 7.

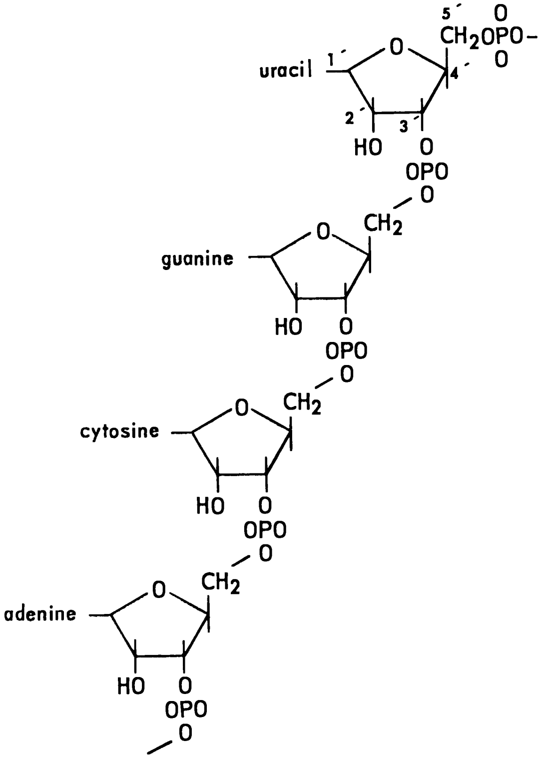
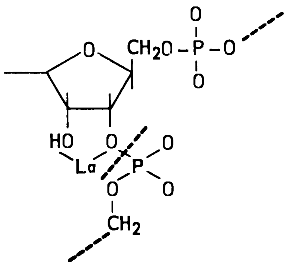


Figure 7. Portion of RNA structure

Various enzymes are capable of degrading the RNA polymer by splitting the bonds between ribose and phosphate. The same reaction has been carried out nonenzymatically with lanthanum and cerium(III) nitrates (2); the mechanism of such a reaction probably involves the formation of a lanthanide complex, followed by cleavage of the phosphate bond:



The backbone of the structure of DNA is similar to that of RNA, except that the sugar portion is 2-deoxyribose instead of ribose. There are two deoxyribose phosphate chains, both of which have a helical structure, winding around the same helical axis. The "bases" (in DNA uracil is replaced by its methylated derivative, thymine) are attached to the deoxyribose perpendicular to the helical axis, and the two helices are held together by hydrogen bonding between the bases through oxygen and nitrogen atoms, as shown for adenine and thymine in Figure 8,*A* (49). (The genetic code is contained in the sequence of bases along the DNA chain.) The structure of the DNA molecule can be represented as in Figure 8,*B*. It can be seen that the stability of the molecule is derived from the multiple H-bond interactions, and that the two-stranded helical structure is destroyed when the hydrogen bonds are broken down.

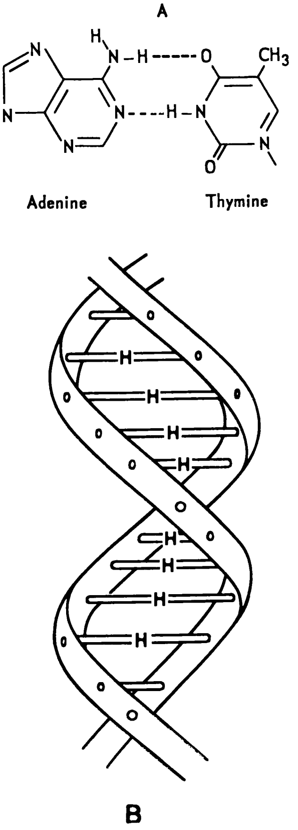


Figure 8. Structure of DNA

A. Hydrogen-bonded base pairing of adenine and thymine
B. Portion of double helix structure (49)

Clearly there are two locations at which metal ions may be bound to the DNA molecule: the phosphate groups on the surface, and the hydrogen-bonded donor atoms in the interior of the structure. These two different modes of metal binding might be expected to produce very different effects on the DNA.

A useful technique for the investigation of these effects is to determine what influence metal ions have upon the splitting of the hydrogen bonds, resulting in the formation of two single strands from the double-stranded molecule. One of the methods for splitting the hydrogen bonds is by heating in aqueous solution. Since the single-stranded molecule absorbs much more strongly than the double-stranded molecule (*14*), the splitting may be followed by looking at the absorption peak at 260 mμ. When absorbance is plotted *vs.* temperature (Figure 9), the absorbance remains constant for a while, then rises abruptly to a maximum. When the solution is cooled, the absorbance goes back down, but not all the way down to its original value. Apparently, on cooling, some of the hydrogen bonds that were severed at the high temperature have reformed. The point in the heating curve at which the absorption increase is half the maximum value is known as T_m, the melting temperature.

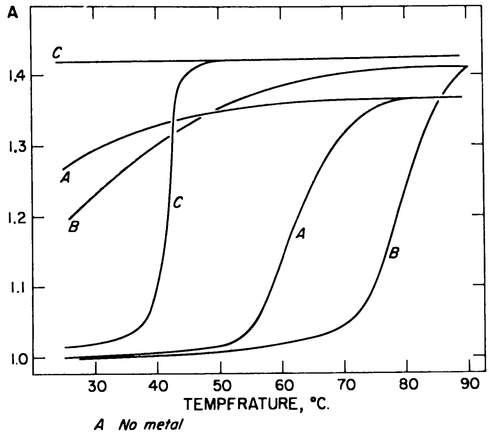


Figure 9. Change in absorbance of DNA solutions on heating and cooling

A. In absence of divalent metal
B. With Mg^{+2}
C. With Cu^{+2}

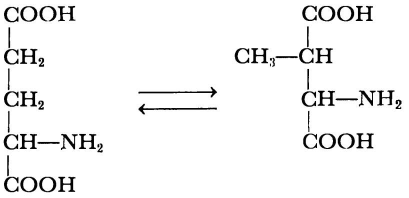
Various divalent metal ions fall into different categories in their effect on the DNA heating and cooling curves (*17*). The alkaline earths and most of the transition metals raise T_m, and increase the extent to which the absorbance decreases on cooling (Figure 9,*B*). Such behavior indicates that these metals stabilize the DNA, since a higher temperature is required to sever the hydrogen bonds, and more of the hydrogen bonds are reformed on cooling. The molecule can be stabilized by neutralization of the negative charges on the phosphate group on the surface of the DNA, since the mutual repulsion of these charges tends to disrupt the molecule. It is believed therefore that the T_m-elevating metal ions are bound to the phosphate.

A second category of metal ions lowers T_m and decreases the extent to which the absorbance is lowered upon cooling. The most drastic effect is with Cu^{+2} (Figure 9,*C*), which decreases T_m more than 20° and yields no decrease of absorbance at all on cooling. Such behavior is best explained by binding to the donor atoms of the "bases" in the interior of the molecule. Such binding would of necessity break the hydrogen bonds and lower T_m. If the H-bonding sites are then occupied by metal ions, none of the H bonds can reform on cooling, thus accounting for the lack of absorbance decrease. It is evident, therefore, that different metal ions can weaken or strengthen the structure of the DNA molecule by binding to different donor atoms within it. Cu^{+2} can be considered a catalyst for the severance of the hydrogen bonds in the molecule.

Other experiments in addition to those cited point to an important role of metal ions in the function of the nucleic acids (*22*, *23*, *38*, *54*, *55*). It has been discovered that RNA is associated with metal ions in the natural state (*47*). Since a dynamic relationship exists between the nucleic acid polymers and monomeric constituents such as ATP, metal ions may play a physiological role in the equilibria that exist between the monomers and the polymers.

Vitamin B_{12} Coenzyme

One substance that has been found to be an essential requirement for the biosynthesis of DNA is the cobalt-containing vitamin B_{12} (*42*). Ever since this substance was first isolated and its structure determined, there has been a widespread search for the specific reactions that it mediates. The first such reaction was discovered by Barker, Weissbach, and Smyth (*5*), when they examined the enzymatic isomerization of glutamic acid to β-methylaspartic acid. They were



$$HOOC{-}CH_2{-}CH_2{-}CH(NH_2){-}COOH \rightleftharpoons HOOC{-}CH(CH_3){-}CH(NH_2){-}COOH$$

Glutamic acid β-Methylaspartic acid

able to isolate a coenzyme, whose structure was elucidated by chemical techniques as a derivative of vitamin B_{12}, in which the cyanide attached to the cobalt has been replaced by adenosine (the riboside of adenine) (*3*, *4*, *24*, *30*, *50*). X-ray diffraction studies by Lenhert and Hodgkin showed that the adenosine is attached to the cobalt through a ribose carbon atom, from which a hydroxyl group had apparently been removed (*32*). The structure is shown in Figure 10.

Undoubtedly this vitamin B_{12} coenzyme is the naturally occurring form of the vitamin, and apparently in the previous isolations of the vitamin the nucleotide was removed and replaced by cyanide. The nature of the attachment of the adenosine, in the form of a carbanion, to the cobalt, is most unusual. It might have been expected that the cobalt would be more likely to bind to one of the nitrogen atoms on the adenine. The oxidation state of the cobalt, which is +3 in the cyanide form of the vitamin (*13*), appears at present to be unknown in the coenzyme (*7*), although magnetic evidence suggests that it is +2 (*6*).

It is of considerable interest to understand under what conditions such an unusual organometallic bond is produced. Not surprisingly, such a bond does not result from the addition of adenosine to the vitamin. It has been demonstrated that the formation of the bond, starting with the hydroxo form of the vitamin, requires ATP (*7*, *51*) (and a metal ion), and that the triphosphate is split from the ATP in two steps (*7*) (Figure 11). In the first step the ATP loses orthophosphate, yielding ADP, which probably becomes bound to the cobalt through the pyro-

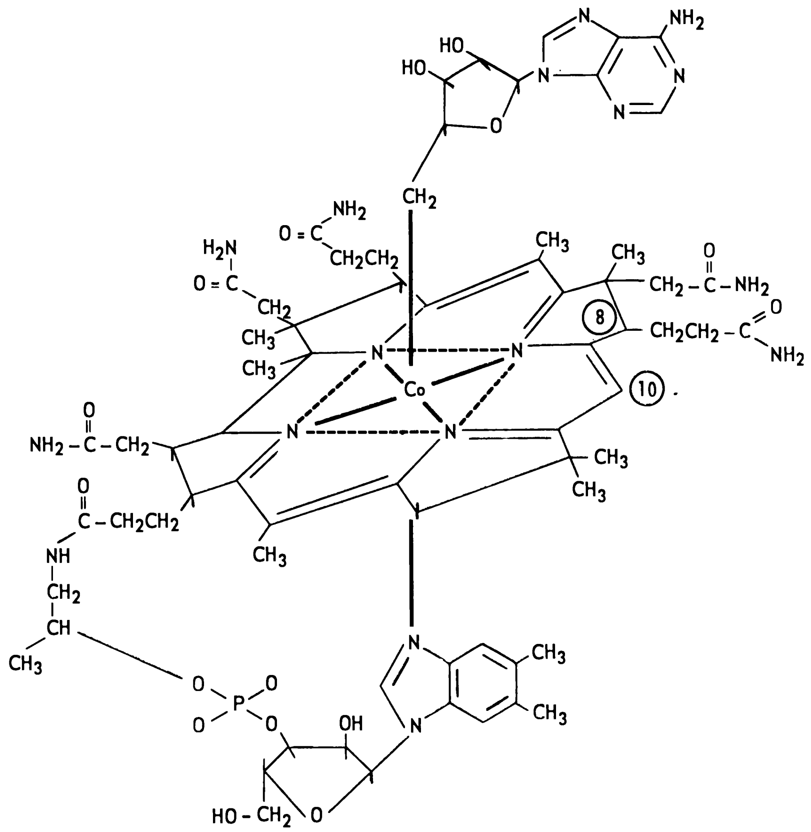


Figure 10. Structure of coenzyme B_{12}

phosphate, and in the second step, the pyrophosphate is removed and the cobalt-carbon bond established. The latter step requires a reducing agent (flavine adenosine dinucleotide) to convert the carbonium ion which presumably is formed when the pyrophosphate splits off, into the carbanion.

It would be interesting to know whether this enzyme system works with cobalt only when the latter is held in the vitamin B_{12} structure, or whether it is possible to produce cobalt-carbon compounds from other cobalt complexes as well.

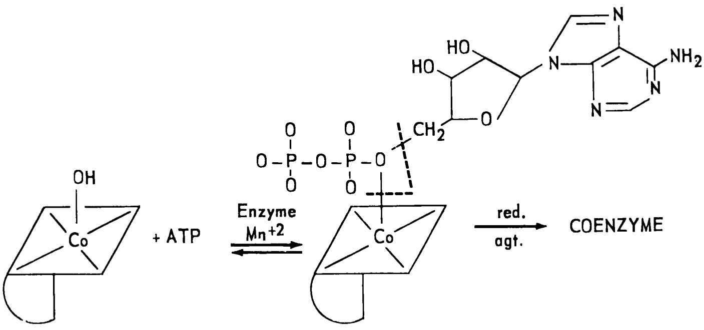
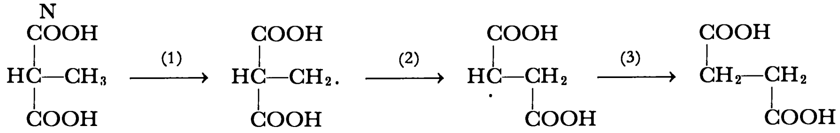


Figure 11. Biosynthesis of coenzyme B_{12} (7)

In addition to the isomerization of glutamic acid, several other coenzyme B_{12}–catalyzed reactions have now been discovered (*1, 9, 15, 31, 51*). The conversion of methylmalonic acid to succinic acid is very similar, and has been shown to occur through the migration of a carboxyl group, and postulated to involve free radical itermediates, as follows (*15*):



$$\begin{array}{c}\mathrm{N}\\\mathrm{COOH}\\|\\\mathrm{HC{-}CH_3}\\|\\\mathrm{COOH}\end{array} \xrightarrow{(1)} \begin{array}{c}\mathrm{COOH}\\|\\\mathrm{HC{-}CH_2.}\\|\\\mathrm{COOH}\end{array} \xrightarrow{(2)} \begin{array}{c}\mathrm{COOH}\\|\\\mathrm{HC{-}CH_2}\\\cdot\quad|\\\mathrm{COOH}\end{array} \xrightarrow{(3)} \begin{array}{c}\mathrm{COOH}\\|\\\mathrm{CH_2{-}CH_2}\\|\\\mathrm{COOH}\end{array}$$

If this scheme is correct, two of the steps in this reaction would require a catalyst: the removal of a hydrogen atom in step 1 and the addition of a hydrogen atom in step 3. The vital question then becomes how the coenzyme B_{12} can participate in this exchange of hydrogens.

One is inclined at first to consider that the cobalt atom is the site of the reaction, but such a condition seems unreasonable in view of the fact that the cobalt is surrounded in the molecule and appears inaccessible. Williams (*36*) has recently called attention to carbon atoms 8 and 10 in vitamin B_{12} by pointing out that these positions lend themselves to a tautomeric shift of a hydrogen from carbon 8, as shown in Figure 10, to carbon 10, with accompanying changes in the double bonds. He also notes that this position may constitute the site for the transfer reactions that are catalyzed by the coenzyme. It would be reasonable that the hydrogen detached from methylmalonic acid in step 1 attached itself to carbon 8 or 10 of the coenzyme. If the cobalt has a +2 oxidation state, a sequence of electron transfers through the ring system could transmit one of the cobalt electrons to the new carbon-hydrogen bond. When the hydrogen is again released from the coenzyme in step 3, the electrons can travel in the reverse direction back to the cobalt. If this mechanism is correct, the cobalt is the storehouse for an electron which can be released and accepted as required. Perhaps the cobalt-carbon bond is peculiarly suited to stabilize such an oxidation-reduction system.

Literature Cited

(1) Abeles, R. H., Lee, H. A., Jr., *J. Biol. Chem.* **236**, PCl (1960).
(2) Bamann, E., Trapmann, H., Fischler, F., *Biochem. Z.* **326**, 89 (1954).
(3) Barker, H. A., Smyth, R. D., Weissbach, H., Munch-Peterson, A., Toohey, J. I., Ladd, J. N., Volcani, B. E., Wilson, R. M., *J. Biol. Chem.* **235**, 181 (1960).
(4) Barker, H. A., Smyth, R. D., Weissbach, H., Toohey, J. I., Ladd, J. N., Volcani, B. E., *Ibid.*, **235**, 480 (1960).
(5) Barker, H. A., Weissbach, H., Smyth, R. D., *Proc. Natl. Acad. Sci.* **44**, 1093 (1958); *J. Biol. Chem.* **235**, 1462 (1960).
(6) Bernhaver, K., Gaiser, P., Müller, O., Müller, E., Gunter, F., *Biochem. Z.* **333**, 560 (1961).
(7) Brady, R. O., Castanera, E. G., Barker, H. A., *J. Biol. Chem.*, **237**, 2325 (1962).
(8) Brenner, S., Streisinger, G., Horne, R. W., Champe, S. P., Barnett, L., Benzer, S., Rees, M. W., *J. Mol. Biol.* **1**, 281(1959).
(9) Brownstein, A. M., Abeles, R. H., *Biol. Chem.* **236**, 1199, 2347 (1961).
(10) Cohen, M., Hughes, T. R., Jr., *Ibid.*, **237**, 176 (1962).
(11) Coleman, J. E., Vallee, B. L., *Ibid.*, **236**, 2244 (1961).
(12) Dickman, S. R., Cloutier, A. A., *Ibid.*, **188**, 379 (1951).
(13) Diehl, H., Van der Haar, R. W., Sealock, R. R., *J. Am. Chem. Soc.* **72**, 5132 (1950).
(14) Doty, P., Boedtker, H., Fresco, J. R., Haselkorn, R., Litt, M., *Proc. Natl. Acad. Sci. U. S.* **45**, 482 (1959).
(15) Eggerer, H., Overath, P., Lynen, F., and Stadtman, E. R., *J. Am. Chem. Soc.* **82**, 2643 (1960).
(16) Eichhorn, G. L., *Federation Proc.* **20**, Suppl. 10, 40 (1961).
(17) Eichhorn, G. L., *Nature* **194**, 474 (1962).
(18) Eichhorn, G. L., Bailar, J. C., Jr., *J. Am. Chem. Soc.* **75**, 2905 (1953).

(19) Eichhorn, G. L., Clark, P., unpublished.
(20) Eichhorn, G. L., Marchand, N. D., *J. Am. Chem. Soc.* **78,** 2688 (1956).
(21) Eichhorn, G. L., Trachtenberg, I. M., *Ibid.*, **76,** 5183 (1954).
(22) Felsenfeld, G., Huang, S., *Biochim. Biophys. Acta* **34,** 234 (1959).
(23) Fuwa, K., Wacker, W. E. C., Druyan, R., Bartholomay, A. F., Vallee, B. L., *Proc. Natl. Acad. Sci. U. S.* **46,** 1298 (1960).
(24) Hogenkamp, H. P. C., Barker, H. A., *J. Biol. Chem.* **236,** 3097 (1961).
(25) Irving, H., Williams, R. J. P., *Nature* **162,** 746 (1948).
(26) Jordan, D. O., "The Chemistry of the Nucleic Acids," Butterworths, Washington, 1960.
(27) Kozloff, L. M., *Record Chem. Progr.* **21,** 49 (1960).
(28) Kozloff, L. M., Lute, M., *J. Biol. Chem.* **228,** 529 (1957).
(29) Kozloff, L. M., Lute, M., Henderson, K., *Ibid.*, **228,** 511 (1957).
(30) Ladd, J. N., Hogenkamp, H. P. C., Barker, H. A., *Ibid.*, **236,** 2114 (1961).
(31) Lengyel, P., Mazumder, R., Ochoa, S., *Proc. Natl. Acad. Sci.* **46,** 1312 (1960).
(32) Lenhert, P. G., Hodgkin, D. C., *Nature* **192,** 937 (1961).
(33) Lowenstein, J. M., *Biochem. J.* **70,** 222 (1958).
(34) Lowenstein, J. M., Shatz, M. N., *J. Biol. Chem.* **236,** 305 (1961).
(35) Malmström, B. G., *Arch. Biochem. Biophys.* **58,** 381, 398 (1955).
(36) Pratt, J. M., Williams, R. J. P., *Biochim. Biophys. Acta* **46,** 191 (1961).
(37) Senoh, S., Tokuyama, Y., Witkop, B., *J. Am. Chem. Soc.*, **84,** 1719 (1962).
(38) Shack, J., Bynum, B., *Nature* **184,** 635 (1959).
(39) Shaw, W. H. R., Raval, D. N., *J. Am. Chem. Soc.* **83,** 3184 (1961).
(40) Smith, E. L., *J. Biol. Chem.* **176,** 997 (1948).
(41) Speck, J. F., *Ibid.*, **178,** 315 (1949).
(42) Spell, W. H., Jr., Dinning, J. S., *J. Am. Chem. Soc.* **81,** 3804 (1959).
(43) Speyer, J. R., Dickman, S. R., *J. Biol. Chem.* **220,** 193 (1956).
(44) Steinberger, R., Westheimer, F. H., *J. Am. Chem. Soc.* **71,** 4158 (1949).
(45) Vallee, B. L., Neurath, H., *J. Biol. Chem.* **217,** 253 (1955).
(46) Vallee, B. L., Williams, R. J. P., Coleman, J. E., *Nature* **190,** 633 (1961).
(47) Wacker, W. E. C., Vallee, B. L., *J. Biol. Chem.* **234,** 3257 (1959).
(48) Warburg, O., Christian, W., *Biochem. Z.* **310,** 389 (1961).
(49) Watson, J. D., Crick, F. H. C., *Nature* **171,** 737 (1953).
(50) Weissbach, H., Ladd, J. N., Volcani, B. E., Smyth, R. D., Barker, H. A., *J. Biol. Chem.* **235,** 1462 (1960).
(51) Weissbach, H., Redfield, Betty, Peterkofsky, Alan, *Ibid.*, **236,** PC40 (1961).
(52) Williams, R. J. P., *Biol. Rev. Cambridge Phil. Soc.* **28,** 381 (1953).
(53) Wold, F., Ballou, C. E., *J. Biol. Chem.* **227,** 301, 313 (1957).
(54) Yamane, T., Davidson, N., *J. Am. Chem. Soc.* **83,** 2599 (1961).
(55) Zubay, G., Doty, P., *Biochim. Biophys. Acta* **29,** 47 (1958).

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4

Ring Substitution Reactions of Metal-Cyclopentadienyls and Metal-Arenes

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The discovery that ferrocene undergoes many ring substitution reactions has led to a rapid and extensive development of a new field of chemistry, metallocene chemistry. Ferrocene will undergo acylation, alkylation, formylation, mercuration, metalation, aminomethylation, sulfonation, and other reactions that are characteristic of a highly reactive aromatic system. π-Cyclopentadienyl derivatives of ruthenium, osmium, manganese, vanadium, and chromium also exhibit certain of these reactions in varying degrees. The π-arene complexes, benzenechromium tricarbonyl and bisbenzenechromium, can be acylated and metalated, respectively. Substituted metallocenes also undergo a variety of unique reactions as well as transformations characteristic of benzenoid derivatives. Acid dissociation constant measurements as well as certain rate and spectral studies indicate pronounced interannular electronic effects in the ferrocene system. Several approaches to the synthesis of biferrocenyl and higher homologs of ferrocene have been explored. Recent rate and stereochemical studies indicate that carbonium ions adjacent to metallocene systems are highly stabilized because of direct metal electron interaction.

One of the most exciting and significant new frontiers of chemistry during the past decade has been the stabilization and study of π-organic derivatives of the transition metals. The borderline nature of this new area between the classical branches of organic and inorganic chemistry has undoubtedly been largely responsible for its rapid development. Moreover, the remarkable synthetic techniques employed for these compounds as well as their properties, structure, and bonding have provided an area of mutual interest shared by experimental and theoretical chemists alike.

Actually, the chemistry of organometallic π-complexes is very old. Compounds containing ethylene coordinated to platinum were isolated by the Danish chemist Zeise as early as 1827 (*129*). This discovery can now be considered to be the origin of organometallic chemistry, predating Frankland's classical isolation of organozinc compounds (*23*) by over 20 years. During the following century and a quarter, however, only scattered reports concerning the isolation of organo-transition metal compounds were described (*12*).

In 1951, the accidental discovery of ferrocene (*42*, *54*) opened up a fertile new branch of chemistry in which many unsaturated ligands other than simple olefins were found to form π-metallo derivatives. Complexes containing the allyl group, cyclobutadiene, the cyclopentadienyl group, arenes, the tropylium group, azulene, cyclo-octatetraene, *ad infinitum* are now known. When one considers the manifold number of unsaturated organic compounds that can serve as π-ligands as well as the number of transition metals, one begins to appreciate the potential magnitude of this new field of chemistry. As a matter of fact, nearly a thousand publications have appeared in the area of organometallic π-complexes in the last ten years.

One path of research resulting from the discovery of ferrocene has been concerned with the synthesis and structural elucidation of cyclopentadienyl derivatives of other metals and metalloids. At the present time, over 60 chemical elements have been found to form one or more cyclopentadienyl compounds. This topic has recently been reviewed by the present author as well as by others (*17*, *83*, *125*).

Another important path of research, especially to organic chemists, resulted from a discovery by Woodward, Rosenblum, and Whiting at Harvard University in 1952 (*128*). These investigators noted the failure of ferrocene to undergo Diels-Alder reactions and its resistance to catalytic hydrogenation. They reasoned that because of its remarkable stability, ferrocene might behave like an aromatic substance. These suppositions proved to be the case, as ferrocene was readily acylated under Friedel-Crafts conditions to form acyl derivatives. Indeed, the name "ferrocene" was given to biscyclopentadienyliron because of its chemical similarity to benzene (*128*).

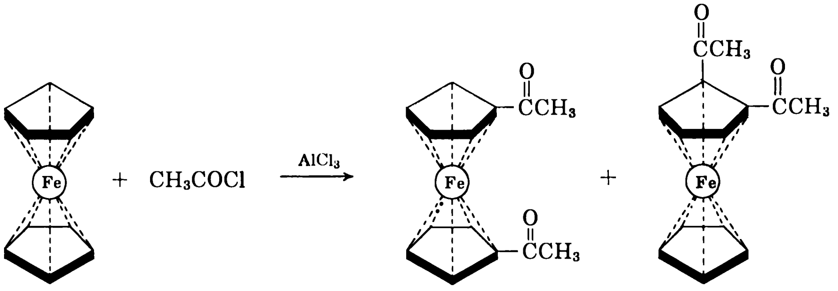
The successful acylation of ferrocene set off a vigorous research effort that has resulted in the establishment of the present field of metallocene chemistry. π-Cyclopentadienyl compounds of ruthenium, osmium, manganese, vanadium, and chromium also exhibit certain aromatic-type reactions in varying degrees. These metallocenes thus represent a new class of heterocyclic compounds in which transition metals, akin to nitrogen, oxygen, and sulfur in classical heterocycles, not only are an integral part of the structure but actually participate directly in many reactions.

Although metallocene chemistry is only 10 years old, the literature is already profuse and cannot be covered in detail in a review of this type. In keeping with the theme of the symposium, attention is focused primarily on the various ring substitution reactions that metallocenes will undergo. In addition, the more significant reactions of substituted metallocenes are presented under the appropriate headings. Finally, important topics dealing with interannular electronic effects in ferrocene, the formation of biferrocenyl and higher homologs of ferrocene, and carbonium ion stabilization adjacent to metallocene nuclei are briefly discussed.

Acylation

The acylation of metallocenes has been the ring substitution reaction most intensively investigated. The Friedel-Crafts reaction between ferrocene and acetyl chloride in the presence of aluminum chloride serves as a good example. When equimolar amounts of these reactants are employed, monoacetylferrocene is formed almost exclusively (*6*, *111*). When an excess of acetyl chloride and aluminum chloride is employed, a mixture of two isomeric diacetylferrocenes is formed, and the products can be separated by careful chromatography on activated alumina (*111*). Nearly all metallocenes are highly colored, as might be expected from compounds containing transition metals, and can be advantageously separated by column chromatography.

The major product is the heteroannular disubstituted derivative, 1,1′-diacetylferrocene (I), while a very small amount of a homoannular isomer, 1,2-diacetylferrocene (II), is also obtained. The first acetyl group therefore appears to deactivate the substituted ring toward further electrophilic substitution, and the second acetyl group preferentially enters the opposite ring.



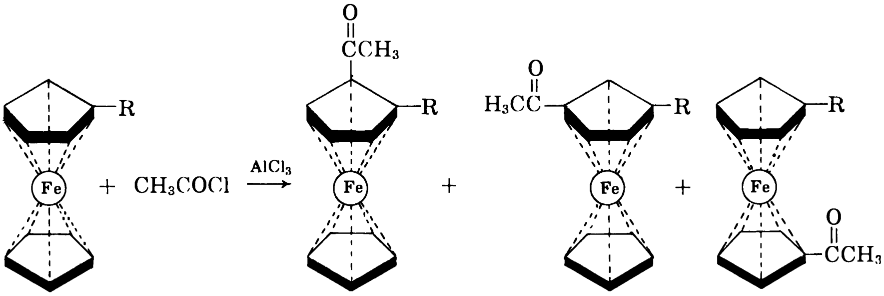
60 parts
I

1 part
II

The structure of I was confirmed by degradative evidence. Under conditions of high temperature and pressure, I was catalytically hydrogenated to ethylcyclopentane to the exclusion of cyclopentane and diethylcyclopentane (*64*). The structure of II was shown by haloform oxidation to the diacid, followed by facile anhydride formation (*94*).

The exceedingly high reactivity of ferrocene to Friedel-Crafts acylation is exemplified by the fact that mild catalysts such as stannic chloride (*63*), boron trifluoride (*32*), zinc chloride (*86*), and phosphoric acid (*29*), can be used with considerable success. When ferrocene and anisole were allowed to compete for limited amounts of acetyl chloride and aluminum chloride, acetylferrocene was the sole product isolated, again illustrating the high reactivity of ferrocene toward electrophilic reagents (*6*).

The acylation of substituted ferrocenes has also received increasing attention in recent years. The nature of the substituent markedly affects the location of the entering acetyl group. Acetylation of monoethylferrocene, for example, produces three isomeric acetylethylferrocenes: the 1,2-isomer (III, R = C_2H_5), the 1-3-isomer (IV, R = C_2H_5), and the 1,1′-isomer (V, R = C_2H_5) (*111*).



III.
$R = C_2H_5$; 1.4
$R = C_6H_5$; 0.77

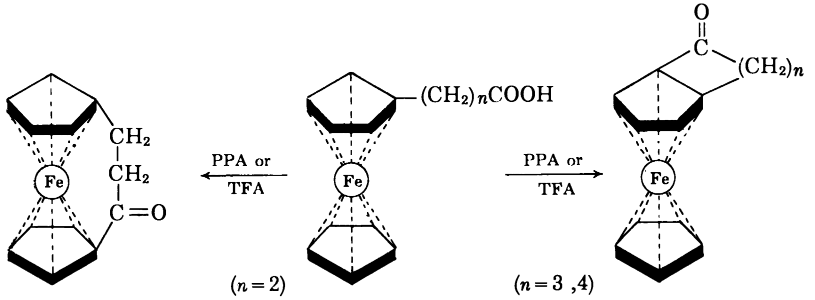
IV.
$R = C_2H_5$; 4.2
$R = C_6H_5$; 0.47

V.
$R = C_2H_5$; 1.0
$R = C_6H_5$; 1.0

The isolation of three isomers of this type is completely consistent with the concept that the two cyclopentadienyl rings in ferrocene are rotating in all but the crystalline state. From the amounts of each isomer formed and the number of nonequivalent ring positions, site reactivities can be calculated, the 1′-position being arbitrarily assigned a value of unity.

From the site reactivities given under each isomer, it can readily be seen that acylation is enhanced in the substituted ring compared to the unsubstituted ring, as might be expected by the presence of an electron-releasing alkyl group. Further, substitution at the 3-position is favored over the 2-position. This result is corroborated by similar studies involving the acetylation of 1,1′-dimethylferrocene, in which it was found that the 3-position was also favored (*105*). Acylation at the 3-position was even more pronounced in the case of 1,1′-diisopropylferrocene, suggesting that steric factors play an important role in determining the mechanism of homoannular acylation of alkylferrocenes.

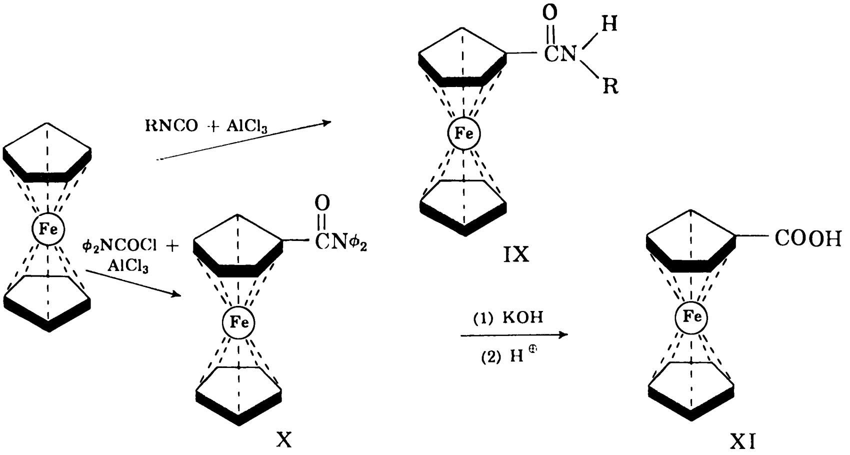
While the acetylation of phenylferrocene also produces three similar acetylphenylferrocenes (III, IV, V; $R = C_6H_5$) (as well as a very small amount of an isomer in which the phenyl group is acetylated), the site reactivities are different (*108*, *109*). The ring bearing the phenyl substituent is deactivated compared to the unsubstituted ring. In contrast to alkylferrocenes, the 2-position is favored over the 3-position. It has been postulated that this is the result of enhanced resonance stabilization of the transition state in substitution involving electrophilic attack at the 2-position.



VII VI VIII

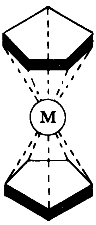
Another interesting series of reactions involving acylation concerns bridging or cyclization of ω-ferrocenylcarboxylic acids. β-Ferrocenylpropionic acid (VI, $n = 2$), when treated with either polyphosphoric acid or trifluoroacetic anhydride, yields the bridged ketone 1,1′-α-ketotrimethyleneferrocene (VII) (*102*). Ferrocenylbutyric or valeric acids (VI, $n = 3, 4$) produce homoannular cyclized products (VIII, $n = 3, 4$). By means of related sequences of reactions, ferrocenes containing two and three trimethylene bridges have now been prepared (*100*, *115*). Indeed, it appears that the interesting situation may soon arise in which the centrosymmetric iron atom is completely enclosed in an "alkylene cage"!

While metallocenes are usually acetylated with acid halides, acid anhydrides, or carboxylic acids, a number of other acylating agents have been reported. The reaction of ferrocene with various isocyanates and aluminum chlorides leads to *N*-substituted ferrocenecarboxamides (IX) (*89*). Use of ruthenocene in place of ferrocene leads to analogous results (*88*). The preparation of *N*-phenylferrocenecarboxamide from phenyl isocyanate in this manner has been used as a proof of structure for the product obtained from the Beckmann rearrangement of benzoylferrocene oxime (*124*).

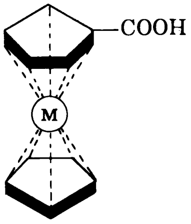


A useful synthetic technique involves the acylation of ferrocene with diphenylcarbamyl chloride and aluminum chloride (*50*). The product, diphenylcarbamylferrocene (X), is readily hydrolyzed to ferrocenecarboxylic acid (XI). Acylation of X followed by hydrolysis produces good yields of 1′-acylferrocenecarboxylic acids.

Several years ago Rausch, Fischer, and Grubert found that the ruthenium and osmium analogs of ferrocene—viz., ruthenocene and osmocene—likewise undergo acylation in varying degrees (*88*). Under identical conditions in which the acylation of ferrocene leads solely to 1,1′-diacylferrocenes, mixtures of mono- and diacylruthenocenes were obtained from ruthenocene acylations, and osmocene yielded only monoacylation products. These studies as well as competition studies indicate that the electrophilic reactivity of Group VIII metallocenes markedly decreases proceeding from ferrocene to osmocene. Further, ruthenocenecarboxylic acid is nearly twice as acidic as is its iron analog (XI).



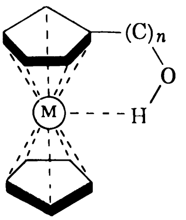
decreasing Friedel-Crafts reactivity →
M = Fe, Ru, Os



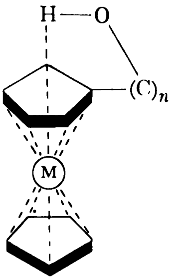
increasing acidity →
M = Fe, Ru

Recently other workers have defined several types of hydrogen bonding in metallocenyl alcohols (*37*, *119*). Hydrogen bonding between the hydroxyl hydrogen and the central metal atom becomes stronger, proceeding from the ferrocenyl to the osmocenyl alcohol. Hydrogen bonding to the π-electron system of the cyclopentadienyl ring appears conversely weaker in ruthenocenyl alcohols compared to ferrocenyl alcohols.

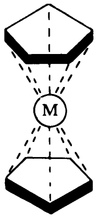
Another interesting comparison of Group VIII metallocenes concerns their ease of protonation in boron trifluoride hydrate (*14*). It appears that the proton is attached directly to the metal atom, and that ruthenocene and osmocene are protonated to a lesser extent than ferrocene.



stronger metal-hydrogen →
bonding, M = Fe, Ru, Os



weaker π-electron-hydrogen →
bonding, M = Fe, Ru



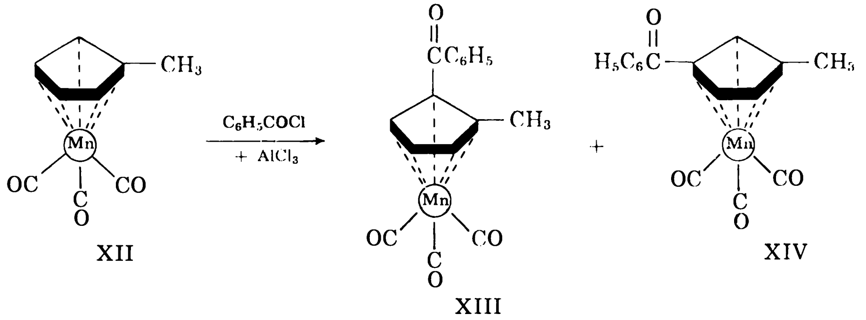
decreasing ease of →
protonation, M = Fe, Ru, Os

It is difficult at present to ascribe all these trends in Group VIII metallocenes to any specific metal effect. It seems, however, that many of the properties of these substances are closely related to the strength of bonding between the central metal atom and the cyclopentadienyl rings. In both metal-olefin chemistry and classical coordination chemistry, for example, the strength of a metal-ligand bond increases, proceeding from the lighter to the heavier metals within a given subgroup (Fe, Ru, Os; Ni, Pd, Pt; etc.). One might likewise expect stronger ring-metal bonding to occur in, say, osmocene compared to ferrocene, as a result of enhanced back-donation from the more readily polarized electrons of the heavier metal to the ring antibonding orbitals compared to the lighter metal. In this regard, infrared (*48*, *88*), thermochemical (*19*), and mass spectral (*24*) studies are in accord with the concept of stronger metal-ring bonding in ruthenocene and osmocene compared to ferrocene.

The protonation studies are of interest in another connection. If protonation of metallocenes can be considered to be a simple form of electrophilic attack, it is possible that other types of electrophilic substitution reactions may proceed through initial coordination of the electrophile with the central metal atom (*14*, *93*). The mechanism of acylation of metallocenes may therefore be more complex than might be expected by analogy to similar reactions of benzenoid compounds. Clearly more studies are needed along these lines, better to define specific metal effects on the properties and reactions of these remarkable compounds.

Acylmetallocenes undergo many reactions shown by acylbenzenes (*35*, *87*, *91*, *116*, *124*), but a detailed discussion is not presented here. Reductions with either lithium aluminum hydride or sodium borohydride give the corresponding carbinols, while Clemmensen reduction, reduction with lithium aluminum hydride plus aluminum chloride, catalytic hydrogenation, etc., yield corresponding alkyl derivatives. Acetylferrocenes undergo a variety of base condensation reactions and can be oxidized to ferrocenecarboxylic acids without apparent oxidation of the iron atom.

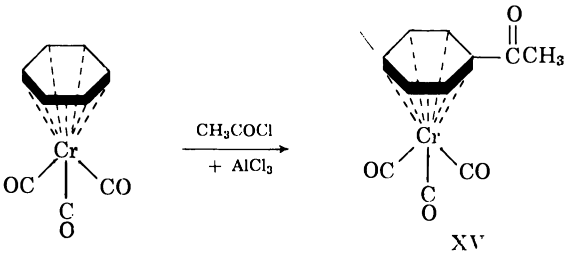
Still other π-cyclopentadienyl–metal compounds have been shown to undergo acylation. The successful acylation of cyclopentadienylmanganese tricarbonyl has opened up yet another interesting aromatic-type system for exploration (*9*, *10*, *11*, *13*, *20*, *45*, *99*). An example of this type concerns the benzoylation of methylcyclopentadienylmanganese tricarbonyl (XII) (*10*, *45*). Both 1-methyl-2-benzoylcyclopentadienylmanganese tricarbonyl (XIII) and the corresponding 1,3-isomer (XIV) are readily obtained.



Cyclopentadienylvanadium tetracarbonyl (*21*, *97*) and cyclopentadienylchromium dicarbonyl nitrosyl (*22*) can also be acylated under Friedel-Crafts conditions.

Attempts to bring about acylation reactions of bisbenzenechromium and bistoluenechromium have thus far failed, the ring-metal bond being readily cleaved under the reaction conditions involved (*25*). On the other hand, benzenechromium tricarbonyl has recently been acylated to produce acetophenonechromium tricarbonyl (XV), the ring-metal bond in this case remaining intact (*15*, *96*).

The failure of various π-cyclopentadienyl–metal and π-arene–metal complexes to undergo aromatic-type substitution reactions does not necessarily mean

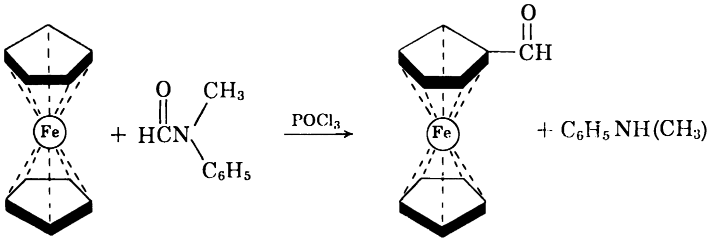


XV

that these systems are devoid of aromatic character. Many such complexes decompose under the usual reaction conditions required for substitution.

Formylation

Ferrocene is similar to other highly reactive aromatic systems, in that it is readily formylated by *N*-methylformanilide in the presence of phosphorus oxychloride (*5*, *29*, *107*, *113*, *118*). Only the mono-substituted product, ferrocenecarboxaldehyde (XVI), is produced even when a large excess of formylating agent is used.



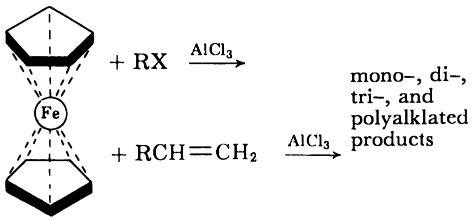
XVI

Ferrocenecarboxaldehyde, like benzaldehyde, is readily reduced to the corresponding carbinol and undergoes the Cannizzaro reaction with alcoholic potassium hydroxide solution. While XVI apparently does not undergo a self-benzoin condensation, it will condense with benzaldehyde to form a mixed benzoin. The low carbonyl stretching frequency (1670 cm.$^{-1}$) of XVI compared to the value for benzaldehyde (1704 cm.$^{-1}$) indicates strong polarization of the carbonyl group. This point is also reflected in the remarkable basicity of XVI, the compound forming a solid hydrochloride from ether solution and dry hydrogen chloride (*5*).

Arnett and Bushick (*2*) have determined the pK_A values for the conjugate acids of ferrocenyl ketones in aqueous sulfuric acid. They have found, for example, that acetylferrocene is over 2000 times more basic than acetophenone and 85 times more basic than *p*-hydroxyacetophenone. These data support the concept that metallocenyl groups are strongly electron-releasing compared to the phenyl group and that they possess extraordinary ability to delocalize adjacent positive charges.

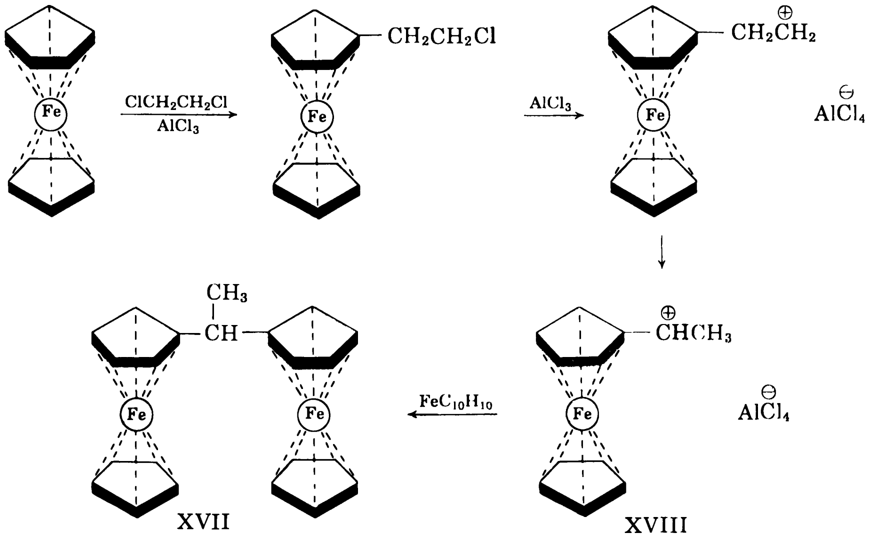
Alkylation

Ferrocene is readily alkylated by alkyl halides, alcohols, or olefins to produce alkylated derivatives (*55*, *122*). The exceedingly great reactivity of ferrocene under these conditions results in the formation of mixtures of mono-, di-, tri-, and polyalkylated products, and the yield of any one alkylation product is usually low. Alkylferrocenes can serve as useful synthetic intermediates, since it has recently been shown that they are conveniently oxidized by activated manganese dioxide



to carbonyl compounds (*101*). Methylferrocene, for example, can be oxidized to ferrocenecarboxaldehyde without apparently oxidizing the iron atom. Another interesting oxidation involves conversion of the 1,1′-dimethylcobalticinium cation to the corresponding dicarboxylic acid cation by means of alkaline potassium permanganate solution (*19*).

The Friedel-Crafts alkylation of ferrocene with ethylene chloride has been the subject of considerable investigation. It was initially reported by Nesmeyanov and coworkers that the reaction produced "diferrocenylethane" and appreciable amounts of polymeric material (*55*). Rinehart and coworkers later proved that the low molecular weight product was 1,1′-diferrocenylethane (XVII) instead of the expected 1,2-isomer (*103*). The anomalous product is postulated to result

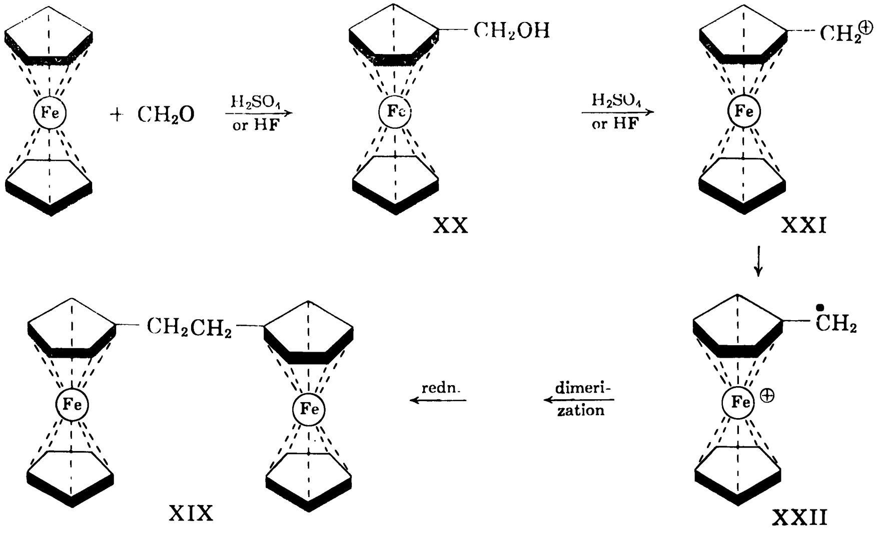


from a hydride ion rearrangement in the transition state, the driving force resulting from the enhanced stability of the α-ferrocenylcarbonium ion (XVIII) compared to the primary carbonium ion formed initially.

Nesmeyanov and coworkers have also recently reported that this reaction produces yet another alkylated product, pentaethylenediferrocene, in which two ferrocene units are purported to be connected by five ethylene bridges (*56*). [This formulation appears highly questionable, since material identical to "pentaethylenediferrocene" has now been isolated by treatment of ferrocene with aluminum chloride in the absence of ethylene chloride (*26*).]

Aldehyde Condensation

The reaction of ferrocene and formaldehyde in either concentrated sulfuric acid or liquid hydrogen fluoride, followed by reduction, produces a compound containing two ferrocenyl and two methylene groups (*57, 98, 123*). After several incorrect assignments had been proposed for the structure of this condensation product, Rinehart and coworkers showed by an unequivocal synthesis that the product was 1,2-diferrocenylethane (XIX) (*104*). The mechanism of the reaction presumably involves the initial formation of ferrocenylcarbinol (XX) followed by ionization in the strongly acidic medium to the ferrocenylmethylcarbonium ion (XXI). Conversion to radical ion XXII followed by dimerization and subsequent reduction produces the product.

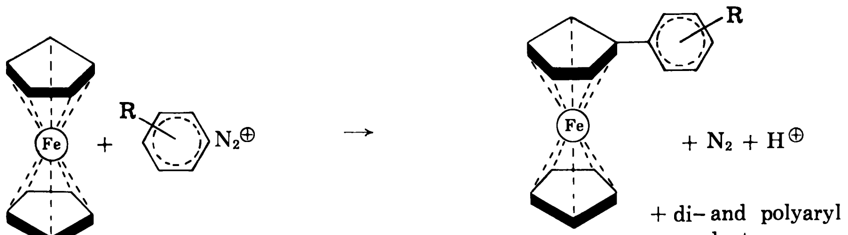


This mechanism is supported by the fact that ferrocenylcarbinol under the same acidic conditions also yields XIX. Further, the intermediate dicationic dimerization product has been isolated as a dipicrate.

Ferrocenecarboxaldehyde and ferrocene also condense to form a deep blue diferrocenylmethine cation. The cation can be isolated in crystalline form as a perchlorate (*40*).

Arylation

The great reactivity of ferrocene toward electrophilic reagents prompted an early examination of its behavior with aryldiazonium salts. Azoferrocenes were expected to be formed by analogy to the reaction of phenol and related reactive aromatic compounds. The reactions instead were found to proceed with elimination of nitrogen and the products were arylferrocenes (XXIII).



XXIII

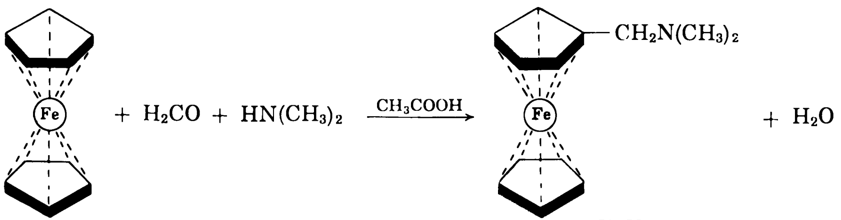
Conversions of this sort now constitute the most convenient means of preparing these substances, an alternative method being direct synthesis from arylcyclopentadienes and iron chlorides (*77*).

Various investigators have studied this reaction using aqueous acetic acid (*7*, *108*) or water-ether mixtures (*62*, *63*) as the solvent. Weinmayr has reported the successful arylation of ferricenium salts in aqueous sulfuric acid (*123*). It is significant that this latter reaction fails in the absence of a small amount of ferrocene (*78*). The products of the arylation reactions are mono-, di-, and polyarylferrocenes. While earlier studies indicated that the diaryl products had a 1,1′-configuration, Rosenblum and coworkers have recently found that all possible structurally isomeric diarylferrocenes (1,1′; 1,2; 1,3) are produced in this manner (*110*). Ferrocene can also be phenylated in cyclohexane solution in the presence of *N*-nitrosoacetanilide (*7*), although the free radical mechanism originally proposed for this reaction and the diazonium arylation is questionable (*110*).

Monosubstituted alkyl-, acyl-, and arylferrocenes undergo arylation to form primarily heteroannular disubstituted ferrocenes (*7*, *79*). Attempts to arylate 1,1′-diacylferrocenes, however, have been reported to result in rupture of the ring-to-metal bond and formation of derivatives of 1,2,3-oxadiazine ring systems (*66*, *79*). [The reaction of 1,1′-diacetylferrocene with benzenediazonium chloride has now been shown to yield 6-methyl-6-hydroxy-2-phenylazofulvene, rather than the originally proposed 1,2,3-oxidiazine structure (*4*).]

Aminomethylation

Hauser and Lindsay first showed that ferrocene undergoes a Mannich-type reaction with formaldehyde and dimethylamine to form dimethylaminomethylferrocene (XXIV) (*31*). This amine is readily converted to a methiodide, and



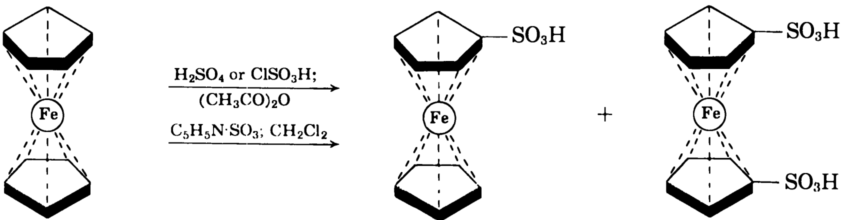
XXIV

the latter quaternary salt has proved to be an important synthetic intermediate in ferrocene chemistry. Reduction of the methiodide of XXIV with sodium amalgam, for example, produces methylferrocene in high yield (*69*). Treatment with solutions of potassium cyanide or potassium hydroxide yields ferrocenylacetonitrile and ferrocenylcarbinol, respectively (*31*, *47*, *76*). Reaction with potassium amide in liquid ammonia results in a Stevens rearrangement to give β-dimethylaminethylferrocene (*33*, *34*).

Aminoethylation of methylferrocene results in substitution apparently at the 3-position (*70*). Pauson and coworkers have reported that aminoethylation of 1,1′-dithiomethylferrocene results in introduction of the dimethylaminomethyl group at both the 2- and 3-positions, the ratio being 1.9 to 1 (*44*).

Sulfonation

Ferrocene can readily be sulfonated by either sulfuric acid or chlorosulfonic acid in acetic anhydride (*43*, *123*). The products, ferrocenesulfonic acid (XXV) and ferrocene-1,1′-disulfonic acid (XXVI), are obtained together with products resulting from oxidation.



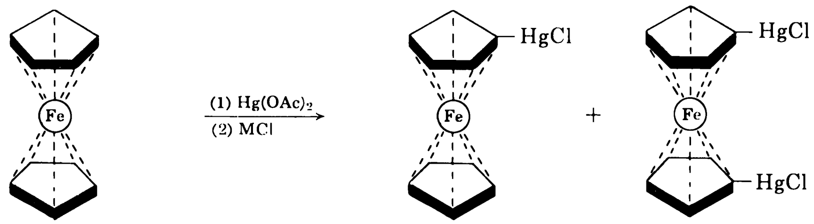
XXV XXVI

A second synthetic technique has employed either pyridine or dioxane adducts of sulfur trioxide as sulfonating agents. Both ferrocene and ferrocenecarboxylic acid have been sulfonated in this manner (*61*, *72*). Cyclopentadienylmanganese tricarbonyl is also readily sulfonated (*10*).

The sulfonic acids of these metallocenes can be converted to sulfonyl chlorides, sulfonamides, etc., by appropriate reagents. Reduction of ferrocenesulfonyl chloride by lithium aluminum hydride produces the rapidly oxidized ferrocenethiol in quantitative yield (*43*). Both the sulfonic acid of cyclopentadienylmanganese tricarbonyl and the corresponding sulfinic acid (obtained by sodium sulfite reduction of the sulfonic acid) have been converted to sulfones (*10*).

Mercuration

Ferrocene, like thiophene, furan, and other so-called "superaromatic" systems, reacts readily with mercuric acetate to form mercurated derivatives. Nesmeyanov and coworkers first reported that ferrocene could be mercurated under relatively mild conditions in either ethyl ether–alcohol or benzene–alcohol solution (*63*). The acetoxymercuriferrocenes formed in this manner are usually treated with an alcoholic solution of an alkali metal halide. The resulting products, chloromercuriferrocene (XXVII) and 1,1′-di(chloromercuri)ferrocene (XXVIII), can be conveniently separated by extraction with n-butyl alcohol.

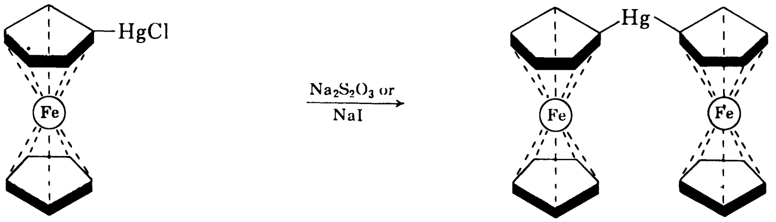


XXVII XXVIII

In a more detailed study of this reaction, Rausch, Vogel, and Rosenberg determined optimum conditions for the synthesis of either XXVII or XXVIII (*90*). Ruthenocene has also been mercurated using glacial acetic acid as the solvent, but pure products could not be separated (*88*).

Mercurated ferrocenes have proved to be useful intermediates in the synthesis of various halogenated ferrocenes. Iodoferrocene, for example, is readily formed by treatment of XXVII with iodine, followed by decomposition of the resulting iodine complex with aqueous sodium thiosulfate (*67*). Dihaloferrocenes can be prepared in low yield, starting with XXVIII and either iodine or bromine. This indirect route to haloferrocenes, as well as the method involving cupric halide cleavage of ferrocenylboronic acids, has been of much value in ferrocene chemistry. Attempts to bring about halogenation directly lead either to halogen-containing complexes or oxidative rupture of the ring-metal bond with formation of pentahalocyclopentanes (*64*, *67*, *98*).

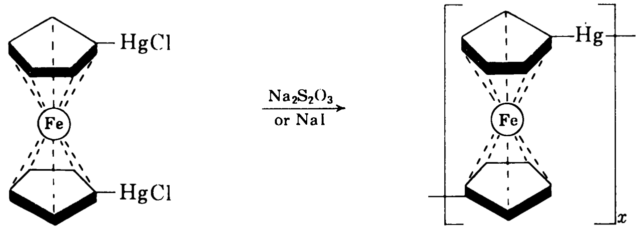
A well-known reaction in organomercury chemistry consists of the conversion of arylmercuric chlorides to diarylmercury compounds by means of solutions of sodium iodide or sodium thiosulfate. Treatment of chloromercuriferrocene readily produces diferrocenylmercury (XXIX) under these conditions (*63*, *90*).



XXIX

Both chloromercuriferrocene and diferrocenylmercury undergo metal interchange reactions with organolithium reagents to form ferrocenyllithium (*81*, *117*). Ferrocenyl Grignard reagents can also be prepared by the reaction of haloferrocenes and magnesium under controlled conditions (*112*).

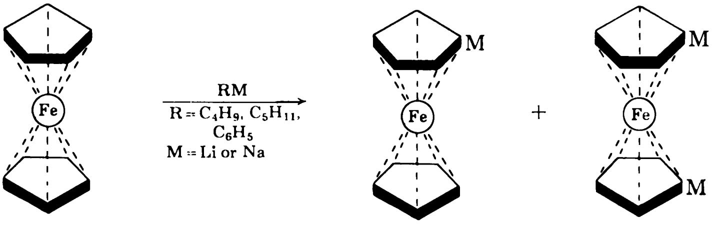
Reaction of 1,1′-di(chloromercuri)ferrocene with sodium iodide or sodium thiosulfate might be expected to lead to higher homologs of XXIX in which ferrocene units are bridged by atoms of mercury. Reactions of this type have produced apparently polymeric materials with structures such as XXX, although the very limited solubility of the products has thus far precluded reliable molecular weight measurements (*80*).



XXX

Metalation

Another very important ring substitution reaction of ferrocene is its ability to undergo metalation with organolithium and organosodium compounds. Metalation with *n*-butyllithium in ethyl ether, first reported by Nesmeyanov and coworkers (*63*) and independently by Benkeser, Goggin, and Schroll (*3*), leads to rather low yields of ferrocenyllithium (XXXI, M = Li) and 1,1′-ferrocenylenedilithium (XXXII, M = Li). It was subsequently shown by Mayo, Shaw, and



XXXI XXXII

Rausch (*53*) that the use of the mixed solvent ethyl ether—tetrahydrofuran (1:1) leads to greatly improved yields of lithioferrocenes XXXI and XXXII, and this procedure has been extensively used in further synthetic applications.

Similar reactions of ferrocene with phenylsodium or *n*-amylsodium lead to the corresponding sodiated products (XXXI, XXXII, M = Na) (*59, 60*). The steric course of both metalation reactions has been studied, and it has been proved that dimetalation occurs in opposite cyclopentadienyl rings (*28*).

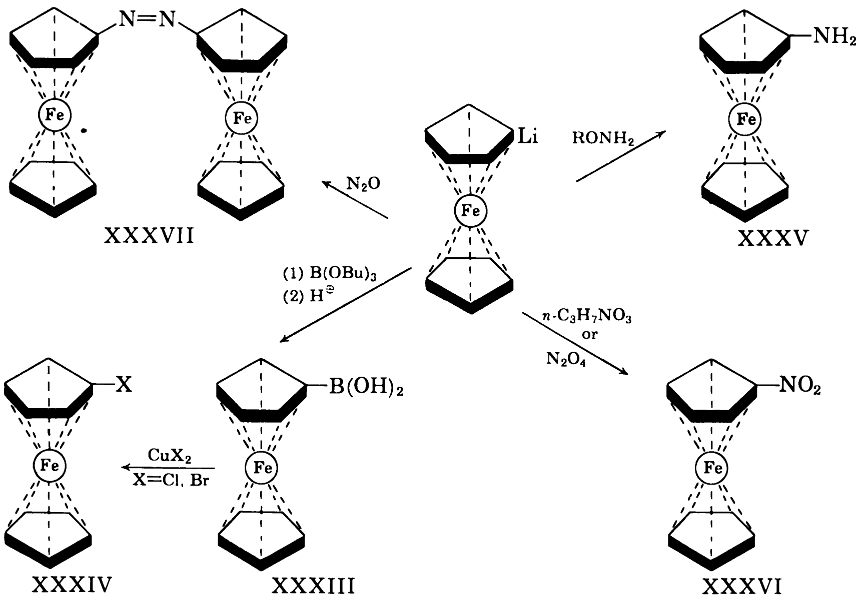
Several investigations have been directed at the metalation of substituted ferrocenes (*60, 106*). Rinehart and coworkers have recently found that 1,1′-dimethylferrocene is metalated in the ring and not at the methyl group, in contrast to the metalation of toluene.

Both ruthenocene and osmocene have been metalated with *n*-butyllithium (*88*). Under comparable conditions ruthenocene is metalated to a greater extent than ferrocene.

Carbonation and subsequent hydrolysis of either lithiated or sodiated metallocenes lead to the corresponding carboxylic acids. Ferrocenecarboxylic acid and ferrocene-1,1′-dicarboxylic acid are readily produced in this manner and can be conveniently separated by extraction of the former with ethyl ether or benzene. The reaction of metalated ferrocenes with various chlorosilanes has led to a variety of triaryl- or trialkylsilylferrocenes (*3, 28, 90*).

Metalated ferrocenes have served as valuable intermediates for the synthesis of a number of other derivatives. Treatment of lithiated ferrocenes with tributyl borate followed by hydrolysis leads to ferroceneboronic acid (XXXIII) as well as the diboronic acid (*73*). Ferroceneboronic acid, like benzeneboronic acid, is readily cleaved by cupric bromide or cupric chloride to form the corresponding halo derivatives (XXXIV). Ferrocene-1,1′-diboronic acid reacts in the same manner, and either one or two carbon-boron bonds can be cleaved. Further reactions of this type have led to a variety of mixed dihaloferrocenes (*73, 75*).

Another important reaction of XXXIII and of XXXIV consists of their facile conversion to ferrocenyl acetate on treatment with cupric acetate. Ferrocenyl acetate in turn has been hydrolyzed to hydroxyferrocene, the ferrocene analog of phenol (*74*).



Aminoferrocene (XXXV) can be prepared in low yield by treatment of *O*-methylhydroxylamine or *O*-benzylhydroxylamine with ferrocenyllithium (*1*, *65*). Nitroferrocene (XXXVI), unattainable by direct nitration of ferrocene, can be isolated from the reaction of ferrocenyllithium and either *n*-propyl nitrate or dinitrogen tetroxide at −70° (*30*, *36*). A similar reaction between ferrocenyllithium and nitrous oxide leads to azoferrocene (XXXVII) (*68*).

Although attempts to acylate bisbenzenechromium under Friedel-Crafts conditions have thus far resulted in cleavage of the ring-metal bond, the successful metalation of this π-arene complex has been recently reported, using amylsodium (*16*). The resulting dimetalated product has been characterized as a dicarbmethoxy derivative, although the position of the two substituents has not yet been determined.

Oxidation and Reduction

Various oxidation and reduction reactions of substituted metallocenes have already been discussed. A large number of substituted metallocenes have been oxidized chronopotentiometrically at a platinum foil in acetonitrile solution (*39*, *46*). Electron-withdrawing substituents decrease the ease of oxidation, while electron-donating substituents increase the ease of oxidation with respect to the parent metallocenes. A plot of chronopotentiometric quarter-wave potentials, $E_{\frac{1}{4}}$, *vs.* Hammett para-sigma constants shows a definite linear relationship. The $E_{\frac{1}{4}}$'s for ruthenocene and osmocene indicate these metallocenes are more difficultly oxidized than ferrocene, in agreement with earlier qualitative observations (*18*).

Ferrocene can also be oxidized to the ferricenium cation, $(FeC_{10}H_{10})^+$, by polarographic oxidation, by chemical oxidizing agents such as ferric chloride or ceric sulfate, or simply by passing air through a suspension of it in concentrated acid (*126*). The deep blue, dichroic cation can readily be reduced to ferrocene by means of reducing agents such as stannous chloride or ascorbic acid (*123*, *126*).

Stronger conditions of oxidation lead to complete rupture of the cyclopentadienyl-iron bond. Attempts to nitrate ferrocene using ethyl nitrate in the presence of sodium alkoxides led to considerable amounts of nitrocyclopentadienylsodium and iron oxides (*118*). Treatment of ferrocene with bromine or chlorine is also reported to result in destruction of the ferrocene nucleus, the products containing pentahalocyclopentanes (*64*).

While initial attempts to hydrogenate ferrocene under relatively mild conditions were not successful, extensive treatment with hydrogen in the presence of a nickel catalyst at 300° to 350° and under 280-atm. absolute pressure results in the formation of cyclopentane (*64*). In contrast to the extreme resistance of ferrocene to catalytic hydrogenation, this aromatic-type compound can be readily reduced by lithium in ethylamine, the products being metallic iron and cyclopentadiene (*121*).

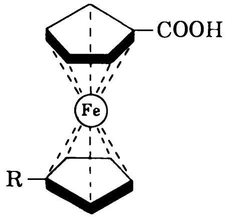
Interannular Electronic Effects

We have seen how a substituent on one cyclopentadienyl ring in ferrocene markedly affects subsequent ring substitution reactions. While certain transformations of this type are at least partially determined by steric factors, it seems certain that resonance and inductive interactions also play a very important role in determining orientation. Electronic transmissions both within and across the cyclopentadienyl rings are not fully understood, since the precise nature of the bonding in ferrocene is still uncertain.

Several additional studies have confirmed interannular electronic interactions in ferrocene. Early investigations by Nesmeyanov and coworkers and by others demonstrated the electron-donor properties of the ferrocenyl group (*71*). Aminoferrocene, for example, is approximately 20 times as strong a base as aniline, while benzoic acid is several times more acidic than ferrocenecarboxylic acid. Moreover, acidities and basicities of this sort are markedly affected by substituents on the opposite cyclopentadienyl ring.

A portion of these data is summarized in Table I, in which the acidities of a number of heteroannular ferrocenecarboxylic acids are compared. Introduction of an electron-releasing alkyl group into the unsubstituted ring lowers the acidity of the corresponding acid, while the introduction of electron-withdrawing groups increases it.

Table I. Interannular Electronic Effects in Ferrocene



R	*pK*A (*68% CH$_3$OH, 20°*)
H	6.29 (C_6H_5COOH, 5.93)
C_2H_5	6.43
C_4H_9	6.50
$COOCH_3$	6.08
$COCH_3$	5.91
CN	5.82
SO_2NH_2	5.56

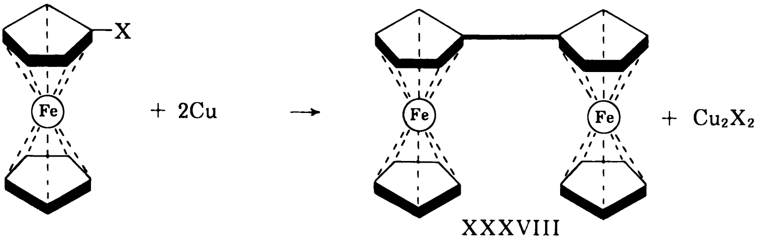
In some related studies, Little and Eisenthal have found that a plot of similarly obtained pK_A values for substituted ferrocenecarboxylic acids *vs.* Hammett para-sigma constants yields a satisfactory straight line (*52*). They have also recently measured the second-order rate constants for the esterification of a series of heteroannular substituted ferrocenecarboxylic acids with diphenyldiazomethane (*51*). Logarithms of the rate constants correlated well with the corresponding acid constants and with Hammett para-sigma constants. These results quantitatively relate interannular electronic effects in ferrocene and suggest that resonance interactions across the cyclopentadienyl rings parallel the effects between substituents in para-substituted benzoic acids.

The carbonyl stretching frequencies of a number of heteroannular ferrocenecarboxylic acids have been measured (*41*). The spectral shifts vary in the direction expected from the electronic effects of the substituent groups, and parallel the effects of these substituents on the acid constants. Little and Clark have also demonstrated resonance interaction of the ferrocenyl group in ferrocenylazobenzenes by measuring shifts in the absorption maxima in the visible and ultraviolet spectra (*49*).

Formation of Biferrocenyl

During studies relating to the synthesis of certain trialkylsilylferrocenes from lithiated ferrocenes and trialkylchlorosilanes, Rausch and coworkers detected minute amounts of a dark orange crystalline substance which was subsequently shown to be biferrocenyl on the basis of analytical evidence (*27, 92*). To provide an unequivocal synthesis and a more satisfactory route to this compound, several alternative routes were investigated.

It was reasoned that if ferrocene behaved as an aromatic system, haloferrocenes should undergo the Ullmann coupling reaction. Biferrocenyl (XXXVIII) was obtained from this reaction and was shown to be identical in every respect with the anomalous material isolated previously (*82, 84*). Somewhat surprisingly, it was found that the reaction of iodoferrocene and copper produces XXXVIII in practically quantitative yield, even at temperatures as low as 60°.

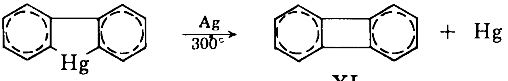


XXXVIII

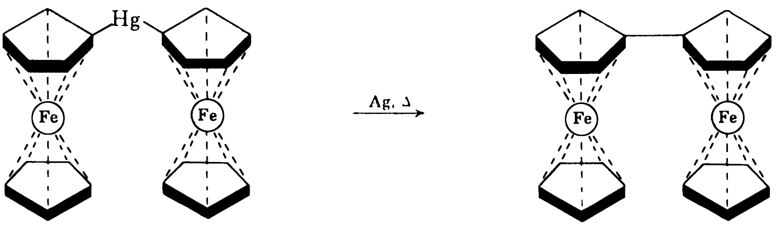
X	*Yield, % (150°)*
I	96–100
Br	97
Cl	65

Additional studies showed that iodoferrocene was approximately as reactive as 1-iodo-2-nitrobenzene under Ullmann conditions. A mixed Ullmann reaction involving these two reactive aryl halides produced 2-nitrophenylferrocene. Ullmann condensations of iodoferrocene with various sodium phenoxides and sodium arenethiolates likewise led to ferrocenyl aryl ethers and sulfides, respectively (*84, 85*).

Another approach to the synthesis of biferrocenyl was suggested by results of Wittig and Herwig (*127*). These investigators found that reaction of *o*-biphenylene-mercury (XXXIX, actually shown to be a cyclic tetramer) and silver when heated at 300° resulted in the elimination of mercury and the formation of biphenylene (XL). Rausch showed that a similar reaction involving diferrocenylmercury and silver at elevated temperatures produced biferrocenyl (XXXVIII) in yields of 30 to 61%, depending on the conditions (*80*, *81*). The other products from the reaction included mercury, ferrocene, and probably polyferrocenylenes.



XXXIX XL



XXXVIII

Nesmeyanova and Perevalova in related studies involving diferrocenylmercury and palladium black obtained similar result (*58*). Their yields of biferrocenyl amounted to only 1 to 6%, however. It is postulated that the reactions proceed via homolytic scission of the carbon-mercury bond with the formation of ferrocenyl radicals.

Biferrocenyl has also been obtained from the interaction of ferroceneboronic acid with ammoniacal silver oxide solution (*74*). Ferrocenyl Grignard reagents decompose at elevated temperatures to give ferrocene and biferrocenyl (*112*). Treatment of ferrocenylmagnesium bromide with cobaltous chloride likewise gives biferrocenyl in high yield (*112*).

α-Metallocenyl Carbonium Ions

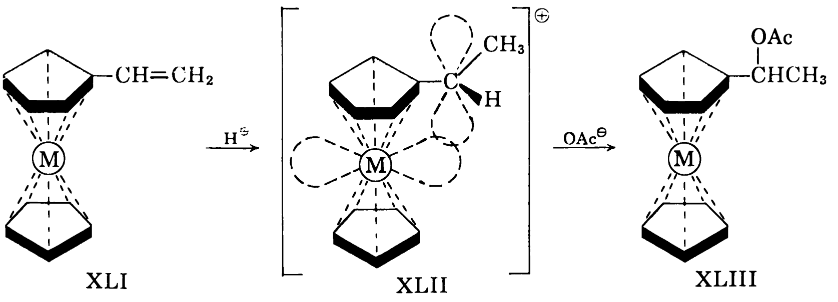
A number of observations have been made which qualitatively suggest that carbonium ions adjacent to metallocene systems possess unusual stability. Ferrocenecarboxaldehyde, for example, is soluble in dilute hydrochloric acid (*5*), ferrocenyl carbinols such as ferrocenyl phenyl carbinol form ethers with great ease (*124*), and ferrocenylmethylcarbinol can be dehydrated to vinylferrocene under exceedingly mild conditions (*114*). The concept of stabilizations of this type has also been used to explain certain anomalous ring substitution reactions.

Richards and Hill have recently obtained quantitative evidence of the stabilization of α-metallocenyl carbonium ions (*38*, *95*). They have shown that solvolyses of methylmetallocenylcarbinyl acetates proceed via a carbonium ion mechanism, and that these acetates solvolyze with rates greater than even triphenylmethyl (trityl) acetate. Further, the relative rates of solvolysis and therefore the order of carbonium ion stabilities increase, proceeding from the iron to the osmium acetate. A portion of these data is summarized in Table II.

Table II. Relative Rates of Solvolysis of Methylmetallocenylcarbinyl Acetates

Acetate	*Relative Rate (80% Acetone, 30°)*
Trityl	0.15
Methylferrocenylcarbinyl	1.00
Methylruthenocenylcarbinyl	1.36
Methylosmocenylcarbinyl	5.37

Buell, McEwen, and Kleinberg have observed that weak acids such as hydrogen azide and acetic acid add readily across the double bond of vinylferrocene (XLI, M = Fe) (*8*). They have postulated that the mechanism of addition proceeds via intermediate formation of the α-ferrocenylcarbonium ion (XLII, M = Fe), followed by conversion to the acetate (XLIII, M = Fe). Stabilization of carbonium ions of this type can result from overlap of filled metal orbitals with the vacant *p*-orbital of the carbonium ion.



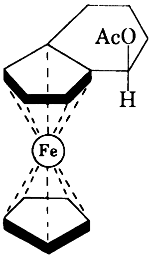
The extraordinary reactivity of vinylferrocene under these conditions prompted a study of the rates of addition of absolute acetic acid to vinylmetallocenes (XLI, M = Fe, Ru, Os). The relative rates are given in Table III.

Table III. Relative Rates of Addition of Acetic Acid to Vinylmetallocenes

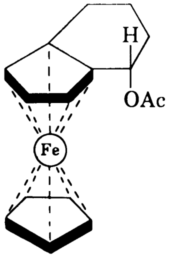
Metallocene	*Relative Rate (100% HOAc, 40°)*
Vinylferrocene	1.00
Vinylruthenocene	1.19
Vinylosmocene	4.62

The relative rate data closely parallel the results obtained in the solvolysis studies. Such a result might be expected from reactions proceeding through similar transition states. The observed order of relative rates may result from better overlap as the size of the central metal atom and the polarizability of its electron shell increase. This would result in increased stabilization and therefore ease of formation of the carbonium ions, proceeding from lighter to heavier metal complexes.

Trifan and Bacskai as well as Hill and Richards have reported the preparation and solvolysis of *exo*-acetate (XLIV and *endo*-acetate (XLV) (*38*, *120*). They showed that the relative rate of solvolysis for XLIV was several thousand times greater than for XLV, indicating it is much more favorable for the acetate group



XLIV



XLV

to leave in a position trans to the metal rather than cis. Metal electrons must therefore be directly participating in backside displacement of the acetate anion in the rate-determining ionization process. The fact that the *exo*-alcohol is the sole alcohol formed from either solvolysis reaction is further evidence of backside metal participation in the transition state.

Literature Cited

(1) Acton, E. M., Silverstein, R. M., *J. Org. Chem.* **24,** 1487 (1959).
(2) Arnett, R. M., Bushick, R. D., *Ibid.,* **27,** 111 (1962).
(3) Benkeser, R. A., Goggin, D., Schroll, G., *J. Am. Chem. Soc.* **76,** 4025 (1954).
(4) Bozak, R. E., Rinehart, K. L., Jr., *Ibid.,* **84,** 1589 (1962).
(5) Broadhead, G. D., Osgerby, J. M., Pauson, P. L., *Chem. and Ind. (London)* **1957,** 209; *J. Chem. Soc.* **1958,** 650.
(6) Broadhead, G. D., Osgerby, J. M., Pauson, P. L., *Ibid.,* **1958,** 650.
(7) Broadhead, G. D., Pauson, P. L., *Ibid.,* **1955,** 367.
(8) Buell, G. R., McEwen, W. E., Kleinberg, J., *Tetrahedron Letters,* No. **5,** 16 (1959); *J. Am. Chem. Soc.* **84,** 40 (1962).
(9) Cais, M., Feldkimel, M., *Tetrahedron Letters,* No. **13,** 440 (1961).
(10) Cais, M., Kozikowski, J., *J. Am. Chem. Soc.* **82,** 5667 (1960).
(11) Cais, M., Modiano, A., *Chem. and Ind. (London)* **1960,** 202; *Tetrahedron Letters,* No. **18,** 31 (1960).
(12) Cotton, F. A., *Chem. Revs.* **55,** 551 (1955).
(13) Cotton, F. A., Leto, J. R., *Chem. and Ind. (London)* **1958,** 1592.
(14) Curphey, T. J., Santer, J. O., Rosenblum, M., Richards, J. H., *J. Am. Chem. Soc.* **82,** 5249 (1960).
(15) Ercoli, R., Calderazzo, F., Mantica, E., *Chim. e Ind. (Milan)* **41,** 404 (1959).
(16) Fischer E. O., Brunner, H., *Z. Naturforsch.* **16b,** 406 (1961).
(17) Fischer, E. O., Fritz, H. P., *Adv. Inorg. Chem. Radiochem.* **1,** 55 (1959).
(18) Fischer, E. O., Grubert, H., *Chem. Ber.* **92,** 1517 (1961).
(19) Fischer, E. O., Herberich, G. E., *Ibid.,* **94,** 1517 (1961).
(20) Fischer, E. O., Plesske, K., *Ibid.,* **91,** 2719 (1958); **92,** 2841 (1959).
(21) *Ibid.,* **93,** 1006 (1960).
(22) *Ibid.,* **94,** 93 (1961).
(23) Frankland, E., *Ann.* **71,** 171, 213 (1849).
(24) Friedman, L., Irsa, A. P., Wilkinson, G., *J. Am. Chem. Soc.* **77,** 3689 (1955).
(25) Fritz, H. P., Fischer, E. O., *Z. Naturforsch.* **12b,** 65 (1957).
(26) Goldberg, S. I., *J. Am. Chem. Soc.* **84,** 3022 (1962).
(27) Goldberg, S. I., Mayo, D. W., *Chem. and Ind. (London)* **1959,** 671.
(28) Goldberg, S. L., Mayo, D. W., Vogel, M., Rosenberg, H., Rausch, M. D., *J. Org. Chem.* **24,** 824 (1959).
(29) Graham, P. J., Lindsey, R. V., Parshall, G. W., Peterson, M. L., Whitman, G. M., *J. Am. Chem. Soc.* **79,** 3416 (1957).
(30) Grubert, H., Rinehart, K. L., Jr., *Tetrahedron Letters,* No. **12,** 16 (1959).
(31) Hauser, C. R., Lindsay, J. K., *J. Org. Chem.* **21,** 382 (1956); **22,** 355 (1957).
(32) *Ibid.,* p. 482.
(33) Hauser, C. R., Lindsay, J. K., Lednicer, D., *Ibid.,* **23,** 358 (1958).
(34) Hauser, C. R., Lindsay, J. K., Lidnicer, D., Cain, C. E., *Ibid.,* **22,** 717 (1957).
(35) Hauser, C. R., *et al., Ibid.,* **22,** 482 (1957); **23,** 1142 (1958); **25,** 1982 (1960); **26,** 1030, 1795, 1800 (1961).
(36) Helling, J. F., Shechter, H., *Chem. and Ind. (London)* **1959,** 1157.
(37) Hill, E. A., Richards, J. H., *J. Am. Chem. Soc.* **83,** 3840 (1961).
(38) *Ibid.,* p. 4216.
(39) Hoh, G. L., McEwen, W. E., Kleinberg, J., *Ibid.,* **83,** 3949 (1961).

(40) Jutz, C., *Tetrahedron Letters*, No. **21**, 1 (1959).

(41) Kazıtsyna, L. A., Lokshin, B. V., Nesmeyanov, N. A., *Doklady Akad. Nauk SSSR* **127**, 333 (1959).

(42) Kealy, T. J., Pauson, P. L., *Nature* **168**, 1039 (1951).

(43) Knox, G. R., Pauson, P. L., *J. Chem. Soc.* **1958**, 692.

(44) Knox, G. R., Pauson, P. L., Tiers, G. V. D., *Chem. and Ind. (London)* **1959**, 1046.

(45) Kozikowski, J., Maginn, R. E., Klove, M. S., *J. Am. Chem. Soc.* **81**, 2995 (1959).

(46) Kuwana, T., Bublitz, D. E., Hoh, G., *Ibid.*, **82**, 5811 (1960).

(47) Lednicer, D., Lindsay, J. K., Hauser, C. R., *J. Org. Chem.* **23**, 653 (1958).

(48) Lippincott, E. R., Nelson, R. D., *J. Chem. Phys.* **21**, 1307 (1953); *J. Am. Chem. Soc.* **77**, 4990 (1955); *Spectrochim. Acta* **10**, 307 (1958).

(49) Little, W. F., Clark, A. K., *J. Org. Chem.* **25**, 1979 (1960).

(50) Little, W. F., Eisenthal, R., *J. Am. Chem. Soc.* **82**, 1577 (1960).

(51) *Ibid.*, **83**, 4936 (1961).

(52) Little, W. F., Eisenthal, R., *J. Org. Chem.* **26**, 3609 (1961).

(53) Mayo, D. W., Shaw, P. D., Rausch, M. D., *Chem. and Ind.* (*London*) **1957**, 1388.

(54) Miller, S. A., Tebboth, J. A., Tremaine, J. F., *J. Chem. Soc.* **1952**, 632.

(55) Nesmeyanov, A. N., Kochetkova, N. S., *Doklady Akad. Nauk SSSR* **109**, 543 (1956); **114**, 800 (1957); **117**, 92 (1957); *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1958**, 242.

(56) Nesmeyanov, A. N., Kochetkova, N. S., *Doklady Akad. Nauk SSSR* **126**, 307 (1959); **136**, 1096 (1961).

(57) Nesmeyanov, A. N., Kritskaya, I. I., *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1956**, 253.

(58) Nesmeyanova, O. A., Perevalova, E. G., *Doklady Akad. Nauk SSSR* **126**, 1007 (1959).

(59) Nesmeyanov, A. N., Perevalova, E. G., Beinoravichute, Z. A., *Ibid.*, **112**, 439 (1957).

(60) Nesmeyanov, A. N., Perevalova, E. G., Beinoravichute, Z. A., Malygina, I. L., *Ibid.*, **120**, 1263 (1958).

(61) Nesmeyanov, A. N., Perevalova, E. G., Churanov, S. S., *Ibid.*, **114**, 335 (1957).

(62) Nesmeyanov, A. N., Perevalova, E. G., Golovnya, R. V., *Ibid.*, **99**, 539 (1954).

(63) Nesmeyanov, A. N., Perevalova, E. G., Golovnya, R. V., Nesmeyanova, O. A., *Ibid.*, **97**, 459 (1954).

(64) Nesmeyanov, A. N., Perevalova, E. G., Golovnya, R. V., Nikitina, T. V., Simukova, N. A., *Izvest Akad. Nauk SSSR, Otdel. Khim. Nauk* **1956**, 739.

(65) Nesmeyanov, A. N., Perevalova, E. G., Golovnya, R. V., Shilovtseva, L. S., *Doklady Akad. Nauk SSSR* **102**, 535 (1955).

(66) Nesmeyanov, A. N., Perevalova, E. G., Golovnya, R. V., Simukova, N. A., Starovsky, O. V., *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, **1957**, 638.

(67) Nesmeyanov, A. N., Perevalova, E. G., Nesmeyanova, O. A., *Doklady Akad. Nauk SSSR* **100**, 1099 (1955).

(68) Nesmeyanov, A. N., Perevalova, E. G., Nikitina, T. V., *Tetrahedron Letters*, No. **1**, 1 (1960).

(69) Nesmeyanov, A. N., Perevalova, E. G., Shilovtseva, L. S., Beinoravichute, Z. A., *Doklady Akad. Nauk SSSR* **121**, 117 (1958).

(70) Nesmeyanov, A. N., Perevalova, E. G., Shilovtseva, L. S., Ustynyuk, Y. A., *Ibid.*, **124**, 331 (1959).

(71) Nesmeyanov, N. A., Reutov, O. A., *Ibid.*, **115**, 518 (1958); *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, **1959**, 926.

(72) Nesmeyanov, N. A., Reutov, O. A., *Ibid.*, **1959**, 926.

(73) Nesmeyanov, A. N., Sazonova, V. A., Drozd, V. N., *Doklady Akad. Nauk SSSR* **126**, 1004 (1959).

(74) Nesmeyanov, A. N., Sazonova, V. A., Drozd, V. N., *Ibid.*, **129**, 1060 (1960); **130**, 1030 (1960); *Tetrahedron Letters*, No. **17**, 13 (1959).

(75) Nesmeyanov, A. N., Sazonova, V. A., Drozd, V. N., Nikonova, L. A., *Doklady Akad. Nauk SSSR* **131**, 1088 (1960).

(76) Osgerby, J. M., Pauson, P. L., *J. Chem. Soc.* **1958**, 656.

(77) Pauson, P. L., *J. Am. Chem. Soc.* **76**, 2187 (1954).

(78) Pauson, P. L., *Quart. Rev.* (*London*) **9**, 391 (1955).

(79) Perevalova, E. G., Simukova, N. A., Nikitina, T. V., Reshetov, P. D., Nesmeyanov, A. N., *Izvest. Akad. Nauk, Otdel. Khim. Nauk* **1961**, 77.

(80) Rausch, M. D., Abstracts of Papers, 140th Meeting, American Chemical Society, Chicago, Ill.. Sept. 3–8, 1961, p. 34-Q.

(81) Rausch, M. D., *Inorg. Chem.* **1**, 414 (1962).

(82) Rausch, M. D., *J. Am. Chem. Soc.* **82**, 2080 (1960).

(83) Rausch, M. D., *J. Chem. Educ.* **37**, 568 (1960).

(84) Rausch, M. D., *J. Org. Chem.* **26**, 1802 (1961).

(85) *Ibid.*, p. 3579.

(86) Rausch, M. D., unpublished studies.

(87) Rausch, M. D., Coleman, L. E., *J. Org. Chem.* **23,** 107 (1958).
(88) Rausch, M. D., Fischer, E. O., Grubert, H., *J. Am. Chem. Soc.* **82,** 76 (1960).
(89) Rausch, M. D., Shaw, P., Mayo, D., Lovelace, A. M., *J. Org. Chem.* **23,** 505 (1958).
(90) Rausch, M. D., Vogel, M., Rosenberg, H., *Ibid.,* **22,** 900 (1957).
(91) *Ibid.,* pp. 903, 1016.
(92) Rausch, M. D., Vogel, M., Rosenberg, H., Mayo, D., Shaw, P., Wright Air Development Center, Tech. Rept. **57–62,** Part II (February 1958); ASTIA Document **150979** (released to Office of Technical Services, U. S. Department of Commerce, Washington 25, D. C., for sale to general public).
(93) Richards, J. H., Abstracts of Papers, 135th Meeting, American Chemical Society, Boston, Mass., April 5–10, 1959, p. 86–O.
(94) Richards, J. H., Curphey, T. J., *Chem. and Ind.* (*London*) **1956,** 1456.
(95) Richards, J. H., Hill, E. A., *J. Am. Chem. Soc.* **81,** 3484 (1959).
(96) Riemschneider, R., Becker, O., Franz, K., *Monatsh.* **90,** 571 (1959).
(97) Riemschneider, R., Goehring, O., Krüger, M., *Ibid.,* **91,** 305 (1960).
(98) Riemschneider, R., Helm, D., *Chem. Ber.* **89,** 155 (1956).
(99) Riemschneider, R., Kassahn, H. G., *Z. Naturforsch.* **14b,** 348 (1959); *Chem. Ber.* **92,** 3208 (1959).
(100) Rinehart, K. L., Jr., Bublitz, D. E., Abstracts of Papers, 141st Meeting, ACS, Washington, D. C., 1962, p. 19–O.
(101) Rinehart, K. L., Jr., Ellis, A. F., Michejda, C. J., Kittle, P. A., *J. Am. Chem. Soc.* **82,** 4112 (1960).
(102) Rinehart, K. L., Jr., Kirby, R. J., *Ibid.,* **79,** 3290 (1957).
(103) Rinehart, K. L., Jr., Kittle, P. A., Ellis, A. F., *Ibid.,* **82,** 2082 (1960).
(104) Rinehart, K. L., Jr., Micheida, C. J., Kittle, P. A., *Ibid.,* **81,** 3162 (1959).
(105) Rinehart, K. L., Jr., Motz, K. L., Moon, S., *Ibid.,* **79,** 2749 (1957).
(106) Rinehart, K. L., Jr., Westman, L., Grubert, H., Gustafson, D. H., Marvel, J. T., Shedroff, T. L., Abstracts of Papers, 17th International Congress of Pure and Applied Chemistry, Munich, Germany, Aug. 30–Sept. 6, 1959, p. 28.
(107) Rosenblum, M., *Chem. and Ind.* (*London*) **1957,** 72.
(108) Rosenblum, M., *J. Am. Chem. Soc.* **81,** 4530 (1959).
(109) Rosenblum, M., Howells, W. G., *Ibid.,* **84,** 1167 (1962).
(110) Rosenblum, M., Howells, W. G., Banerjee, A. K., Bennett, C., *Ibid.,* **84,** 2726 (1962).
(111) Rosenblum, M., Woodward, R. B., *Ibid.,* **80,** 5443 (1958).
(112) Shechter, H., Helling, J. F., *J. Org. Chem.* **26,** 1034 (1961).
(113) Schlögl, K., *Monatsh.* **88,** 601 (1957).
(114) Schlögl, K., Seiler, H., *Naturwissenschaften,* **48,** 376 (1961).
(115) Schlögl, K., Seiler, H., *Tetrahedron Letters,* No. **7,** 4 (1960).
(116) Schlögl, K., *et al., Monatsh.* **88,** 601 (1957); **92,** 219, 533 (1961).
(117) Seyferth, D., Helling, J. F., *Chem. and Ind.* (*London*) **1961,** 1568.
(118) Titov, A. I., Lisitsyna, E. S., Shemtova, M. R., *Doklady Akad. Nauk SSSR* **130,** 341 (1960).
(119) Trifan, D. S., Bacskai, R., *J. Am. Chem. Soc.* **82,** 5010 (1960).
(120) Trifan, D. S., Bacskai, R., *Tetrahedron Letters,* No. **13,** 1 (1960).
(121) Trifan, D. S., Nicholas, L., *J. Am. Chem. Soc.* **79,** 2746 (1957).
(122) Vogel, M., Rausch, M. D., Rosenberg, H., *J. Org. Chem.* **22,** 1016 (1957).
(123) Weinmayr, V., *J. Am. Chem. Soc.* **77,** 3009 (1955).
(124) Weliky, N., Gould, E. S., *Ibid.,* **79,** 2742 (1957).
(125) Wilkinson, G., Cotton, F. A., *Prog. Inorg. Chem.* **1,** 1 (1959).
(126) Wilkinson, G., Rosenblum, M., Whiting, M. C., Woodward, R. B., *J. Am. Chem. Soc.* **74,** 2125 (1952).
(127) Wittig, G., Herwig, W., *Chem. Ber.* **87,** 1511 (1954).
(128) Woodward, R. B., Rosenblum, M., Whiting, M. C., *J. Am. Chem. Soc.* **74,** 3458 (1952).
(129) Zeise, W. C., *Pogg. Ann.* **9,** 632 (1827).

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5

The Chemistry of Quasiaromatic Metal Chelates

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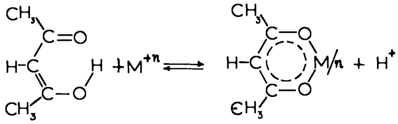
Nondestructive reactions of trisacetylacetonates of chromium(III), cobalt(III), and rhodium(III) are reviewed. Halogenation, nitration, thiocyanation, acylation, formylation, chloromethylation, and aminomethylation take place at the central carbon of the chelate rings. Trisubstituted chelates were obtained in all cases except acylation and formylation. Unsymmetrically and partially substituted chelates have been prepared. Substitutions on partially resolved acetylacetonates yielded optically active products. NMR spectra of unsymmetrically substituted, diamagnetic chelates were interpreted as evidence for aromatic ring currents. Several groups were displaced from the chelate rings under electrophilic conditions. The synthesis of the chromium(III) chelate of malonaldehyde is outlined.

For many years inorganic chemists have studied metal chelates in order to understand the properties of metal ions under the perturbing influence of ligand groups (*2*, *4*, *17*, *21*, *27*, *32*). For example, the metal acetylacetonates (I), have been investigated incessantly since the preparation of the first acetylacetonate in 1887. Such studies have focused on almost every aspect of the physical and chemical properties of the central metal ion in these chelates. On the other hand, organic chemists have respected the traditional schism between organic and inorganic chemistry by considering these chelates as inorganic and thus forbidden substances. The remarkable result of these divergent viewpoints is that in 1958, even though several hundred papers in the literature described the physical properties and preparation of metal acetylacetonates, almost nothing was known about the chemical reactions of the chelate ring itself. This inconsistency is best illustrated by comparison of reviews of metal acetylacetonates written for inorganic (*27*) and for organic chemists (*5*).



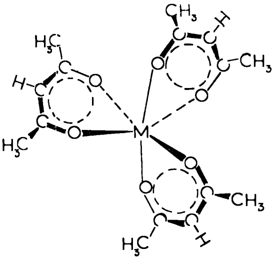
I

M = Cr, Co, Rh

The nature of the bonding in these chelates continues to be the subject of considerable controversy. Calvin and Wilson suggested in 1946 that the unexpected stability of some of these chelates might be ascribed to their aromatic character (*6*). In 1958, Holm and Cotton pointed out that such aromaticity was unreasonable on the basis of the symmetry and energy of the metal orbitals available for π bonding (*22*). Barnum has recently suggested that on the basis of the electronic spectra of these chelates there may be significant π bonding between these ligands and the metal ion (*3*).

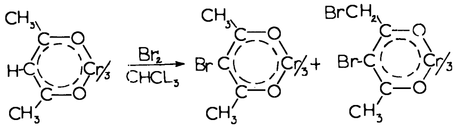
In 1959 a general investigation of the reactions of metal chelate rings was initiated in our laboratories. Its thesis was the chemical elaboration of organic ligands bound in metal chelate rings and the concurrent study of the effect of coordination on the chemical properties of the ligands. It was anticipated that such experiments might lead to the synthesis of new types of coordination compounds, organic heterocycles, and chelate polymers.

To avoid reactions likely to be attended by chelate ring opening, the relatively stable trisacetylacetonates of chromium(III), cobalt(III), and rhodium(III) (II) were chosen as substrates to explore this hypothesis. These kinetically stable nonionic complexes are amenable to treatment in organic solvents where hydrolytic decompositions can be minimized. Furthermore, familiar organic chemical techniques such as crystallization, chromatography, and infrared, ultraviolet, and nuclear magnetic resonance spectra are useful in the characterization and purification of these substances. It was also anticipated that the asymmetric nature of these chelates would be useful in studying the mechanism of ring substitution reactions.



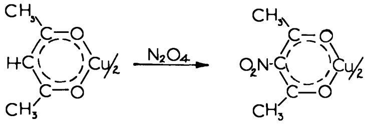
II

A search of the literature revealed two instances in which metal acetylacetonate rings had been substituted without degradation of the chelate rings. Treatment of chromium(III) acetylacetonate with bromine in chloroform had been reported to yield two products—a tribromo- and a hexabromochelate (III and IV) (*31*). These structures were assigned on the basis of halogen analyses. Later work simultaneous with our own revealed that IV was actually a chloroform solvate of III (*24*).



III IV

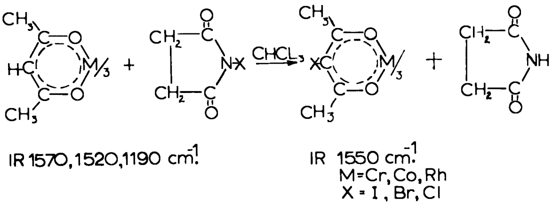
A report (*18*) by Djordjevis, Lewis, and Nyholm in 1959 that reaction of copper acetylacetonate with N_2O_4 afforded bis-(3-nitro-2,4-pentanediono)copper-(II) (V), spurred our early efforts in acetylacetonate chemistry. The nitrochelate was thoroughly characterized.



V

Halogenation

Treatment of a series of metal acetylacetonates with the *N*-halogen succinimides in boiling chloroform afforded the trihalogenated metal chelates in high yields. The use of bromine or iodine monochloride in buffered acetic acid also yielded the bromo- and iodochelates (*7*).



The distinctive infrared spectra of the trihalogenated chelates are useful in the characterization of these complexes (*14*). Whereas the unsubstituted acetylacetonates exhibit two intense bands in the 1500- to 1600-cm.$^{-1}$ region, acetylacetonates with a group other than hydrogen substituted at the central carbon of the chelate ring show a single peak in this region (*19*). Each halogenated chelate exhibits a single peak at about 1550 cm.$^{-1}$ Further, the characteristic in-plane bending mode (*32*) of the ring hydrogen at 1190 cm.$^{-1}$ is absent from all of these products. The presence or absence of this band was used throughout our studies to check for unsubstituted chelate rings.

The proton magnetic resonance spectra (Table I) of the diamagnetic halogenated chelates of cobalt and rhodium exhibited a single sharp signal at about 7.5τ whereas the starting materials produced signals at 4.4 and 7.8τ in the ratio of 1 to 6. These spectra confirm substitution of the ring hydrogen.

Although the halogenated chelates of chromium, cobalt, and rhodium would be difficult to prepare from the sensitive 3-halo-2,4-pentanediones, the copper(II) bromochelate was synthesized both from the bromodiketone and by direct bromination of copper acetylacetonate. The relatively labile copper chelates form much more rapidly than the kinetically stable chelates of chromium, cobalt, and rhodium.

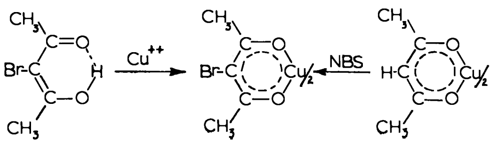
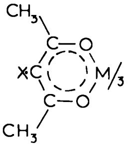
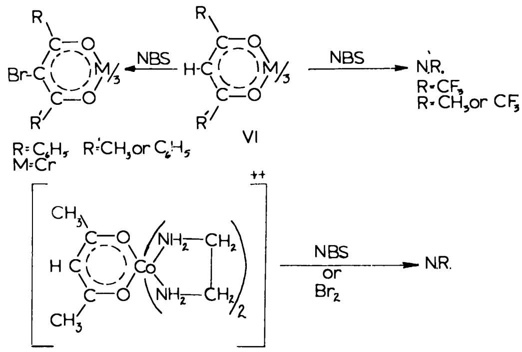


TABLE I. Proton Magnetic Resonance Signals of Symmetrically Substituted Metal Acetylacetonates

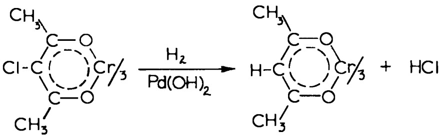


X	*M*	*Solvent*	*Ring H*	*Methyl*
H	Rh	CCl_4	4.65	7.89
H	Rh	$CHCl_3$	4.61	7.86
Cl	Rh	CCl_4	..	7.57
Br	Rh	CCl_4	..	7.49
NO_2	Rh	CCl_4	..	7.59
SCN	Rh	CCl_4	..	7.30
CH_3	Rh	CCl_4	..	7.80
H	Co	C_6H_6	4.63	8.04
H	Co	$CHCl_3$	..	7.81
Cl	Co	C_6H_6	..	7.78
Br	Co	C_6H_6	..	7.70
NO_2	Co	$CHCl_3$	..	7.43

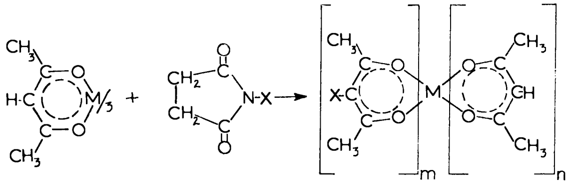
Certain other 1,3-dicarbonyl chelates were brominated with difficulty or not at all. For example, the trifluoro- and hexafluoroacetylacetonates (VI, R = CF_3, R′ = CH_3, and R = R′ = CF_3) were not brominated under a variety of vigorous conditions. However, in the case of the chromium chelates of 1-phenyl-1,3-butanedione and dibenzoylmethane (VI, R = C_6H_5, R′ = CH_5, and R = R′ = C_6H_5), reaction with *N*-bromosuccinimide (NBS) was successful. That the electron density at the central carbon of the chelate ring is an important factor in the success or failure of these electrophilic substitutions is evident from the fact that the bis-(ethylenediamine)-2,4-pentanedionocobalt(III) cation cannot be brominated even under vigorous conditions.



The chemical inertness of the halogen atoms on these chelate rings was surprising and disappointing. These groups failed to react with lithium or magnesium metal or with a variety of nucleophiles except under forcing conditions which resulted in decomposition of the chelate rings. The trichlorochromium acetylacetonate has been catalytically reduced to chromium acetylacetonate.



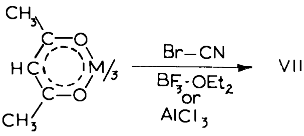
Treatment of these metal acetylacetonates with limited amounts of halogenating agents in dilute solutions afforded complex mixtures of starting materials and mono-, di-, and trihalogenated chelates. These mixtures were separated by alumina chromatography and the partially substituted chelates characterized by infrared and NMR spectra. These mixed-ring chelates (VII) represent the first examples of this type of compound. Because of the inert chemical properties of the chelate ring halogens, these partially halogenated chelates afford routes to mono- or difunctional coordination compounds. Such substances should prove useful in the synthesis of non-cross-linked chelate polymers and in the study of intramolecular, interannular electronic effects. The infrared spectra of these and all other mixed ring acetylacetonates indicate that the vibration of each chelate ring is independent of the other. Martell (*29*) has assumed this vibrational independence in a theoretical analysis of the infrared spectra of metal trisacetylacetonates.



VII

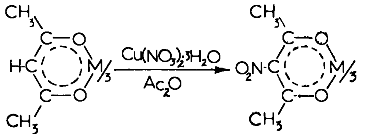
M=Cr,Co,Rh; X=I, Br, Cl
m=1, n=2; m=2, n=1

The mono- and dibrominated chelates were also obtained by reaction of the acetylacetonates with cyanogen bromide in the presence of boron trifluoride etherate or aluminum chloride. In the absence of these Lewis acid catalysts cyanogen bromide does not react with these acetylacetonates. No trace of cyanogenated products was detected from these reactions.



Nitrations

The acid lability of the acetylacetonates of chromium, cobalt, and rhodium prevents their nitration in sulfuric-nitric acid mixtures or in other strongly acidic media. Treatment of chromium acetylacetonate with N_2O_4 yielded complex mixtures of labile nitrogen-containing chromium chelates, but not the desired nitrochelate. Reaction with the $N_2O_4 . BF_3$ complex afforded the chromium nitrochelate (VIII), but in very low yield (*8*). A mixture of copper nitrate and acetic anhydride proved effective in nitrating these chelate rings (*9*, *10*). The trinitrochelates, (VIII, IX, and X) were obtained in high yield by hydrolysis of these reaction mixtures. These chelates are of particular interest since the parent ligand, nitroacetylacetone, is unknown.

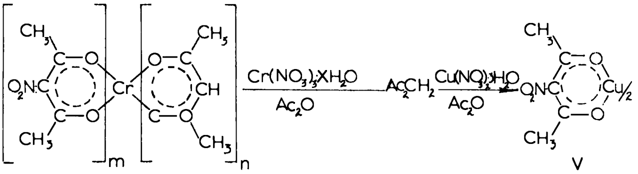


VIII M=Cr
IX M=Co
X M=Rh

IR 1580,1520,1190 cm^{-1} IR 1570,1520,820 cm^{-1}

The infrared spectra of the trinitrochelates were characterized by strong nitro absorptions at 1520 and 825 cm.$^{-1}$ and by the absence of absorption at 1190 cm.$^{-1}$. The NMR spectra of the diamagnetic cobalt and rhodium nitrochelates (IX and X) exhibit a single signal at 7.4τ (*10*), confirming the substitution of all three rings. The low field position of the methyl signal is probably due to a combination of electronegativity and anisotropy of the nitro group.

The unusual copper nitrate–acetic anhydride reagent reacted with acetylacetone itself to form bis-(3-nitro-2,4-pentanediono) copper(II) (V), the same compound prepared by Nyholm (*18*). A novel elaboration of this reaction was treatment of hydrated chromium(III) nitrate with acetylacetone in acetic anhydride to yield a mixture of mono- and dinitrochromiumacetylacetonate (XI and XII).



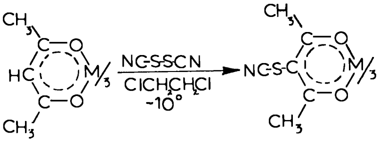
XI m=1, n=2
XII m=2, n=1

V

It is also possible to prepare mono- and dinitrochelates such as XI and XII by use of limited amounts of the nitrating agent. Mixtures of these chelates are conveniently separated by chromatography on specially treated Florisil.

Introduction of Sulfur into Chelate Ring

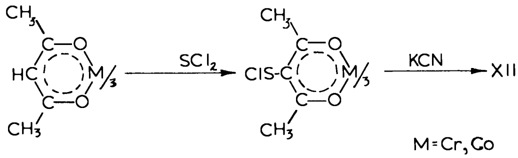
The acetylacetonate ring is attacked by a variety of sulfur electrophiles (*25, 26*). For example, reaction of these chelates with thiocyanogen proceeds smoothly at −10° to give high yields of the tristhiocyanochelates (XIII). The chemical reactivity of the thiocyano groups on these rings has not yet been studied.



M=Rh,Co,Cr

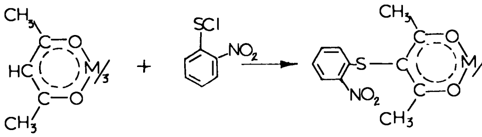
XIII

Sulfur dichloride attacks these chelate rings under mild conditions and the trissulfenyl chloride chelates (XIV) have been reported to react with a variety of alcohols, amines, olefins, and phenol. The products of these reactions have, for the most part, not been purified and characterized, probably because of the bad mixtures resulting from the trifunctional reactant. Treatment of these sulfenyl chlorides with cyanide ion yields the thiocyano derivatives (XIII) (*25*).



XIV

Aryl sulfenyl chlorides attack the acetylacetonate ring without catalysis. The resulting aryl sulfide chelates (XV) are unusual in that they form remarkably stable clathrate complexes with benzene (*26*).

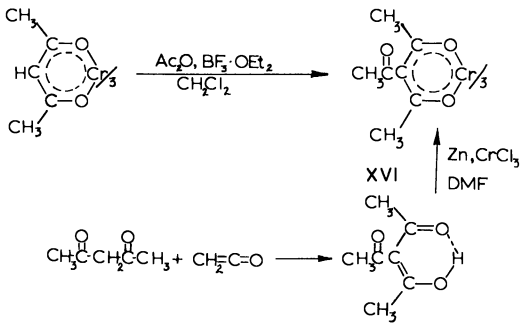


XV

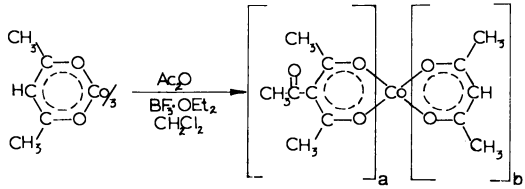
Friedel-Crafts Acylation of Chelate Ring

Friedel-Crafts acylations of the metal acetylacetonate rings are much slower than the electrophilic substitutions described above, probably because of the considerable steric bulk at the reaction site. Furthermore, the strongly acidic conditions during the reaction and subsequent hydrolysis step give rise to considerable degradation, particularly in the case of the more sensitive chromium and cobalt chelates. This consideration places severe limitations on the reaction conditions that can be employed.

Treatment of chromium(III) acetylacetonate with acetic anhydride and boron trifluoride etherate yielded a complex mixture of acetylated chelates but very little starting material. Fractional crystallization and chromatographic purification of this mixture afforded the triacetylated chromium chelate (XVI), which was also prepared from pure triacetylmethane by a nonaqueous chelation reaction (*8*, *11*). The enolic triacetylmethane was prepared by treating acetylacetone with ketene. The sharp contrast between the chemical properties of the coordinated and uncoordinated ligand is illustrated by the fact that chromium acetylacetonate does not react with ketene.

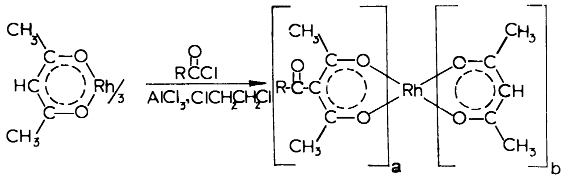


Under the same conditions, cobalt acetylacetonate afforded a mixture of four products: the mono-, di-, and triacetylated chelates (XVII, XVIII, and XIX), along with the starting material. In contrast to the chromium chelates, the mixture of cobalt complexes was cleanly separated by chromatography. The identity of each of these products was established by an NMR spectrum. The presence of uncoordinated carbonyl groups was revealed by infrared absorption at 1675 cm.$^{-1}$



XVII a=1, b=2
XVIII a=2, b=1
XIX a=3, b=0

Rhodium acetylacetonate differed considerably from the other metal chelates in the acetylation reaction (*26*). Under the same conditions that had given extensive acetylation of the cobalt and chromium acetylacetonates, the rhodium chelate reacted very slowly and formed only a small amount of the monoacetylated compound (XX). Fortunately, the hydrolytic stability of rhodium acetylacetonate is such that the Friedel-Crafts reaction can be carried out under vigorous conditions that would rapidly degrade the chromium and cobalt chelates. Thus treatment of rhodium acetylacetonate with acetyl chloride and aluminum chloride in dichloroethane afforded the mono- and diacetylated chelates (XX and XXI). No triacetylated chelate was isolated from this reaction. In a similar manner butyryl- and benzoyl-substituted rhodium chelates (XXIII and XXIV) have been prepared. These and other experiments indicate that the rhodium acetylacetonate ring is less reactive than the cobalt or chromium rings.

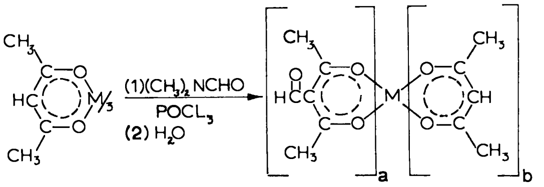


XX a=1, b=2, R=CH_3
XXI a=2, b=1, R=CH_3
XXII a=3, b=0, R=CH_3
XXIII a=1, b=2, R=C_3H_7
XXIV a=1, b=2, R=C_6H_5

Attempted alkylations of these acetylacetonate rings using benzyl and allyl chloride resulted only in the recovery of the starting material.

Formylation of Chelate Ring

The acetylacetonates of chromium, cobalt, and rhodium were found to react with dimethylformamide in the presence of phosphorus oxychloride to yield formyl-substituted chelates (*10*). This is a well known technique for the introduction of an aldehyde group into reactive aromatic systems. The formylation of the chelate rings is a slow reaction, and by controlling the conditions it is possible to form either mono- or diformylated products. Although a small amount of the completely formylated cobalt chelate (XXV) has been detected, it has not been characterized. The mono- and diformylated cobalt chelates (XXVI and XXVII) and the monoformylated chromium and rhodium chelates (XXVIII and XXIX) have been fully characterized.

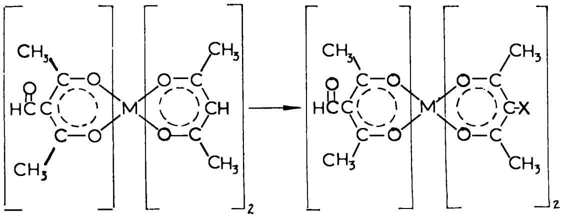


XXV a=3, b=o, M=Co
XXVI a=1, b=2, M=Co
XXVIIa=2, b=1, M=Co
XXVIIIa=1, b=2, M=Cr
XXIX a=1, b=2, M=Rh

The characterization of the aldehyde chelates was hampered by the unusual difficulty encountered in the separation of these reaction mixtures by chromatography and by the sluggish chemical reactivity of the aldehyde groups. Whereas the aldehyde chelates gave positive Tollens tests, characteristic derivatives such as oximes could not be prepared. Furthermore, all attempts at preparative oxidation or reduction of the chelate aldehyde groups either destroyed the chelate rings or resulted in the recovery of the starting material. The infrared spectra of these chelates revealed an uncoordinated carbonyl group, but the frequency (1670 cm.$^{-1}$) of this band was unusually low, even for a conjugated aldehyde.

The NMR spectra of the diamagnetic aldehyde chelates confirmed the assigned structures. The spectrum of the cobalt monoaldehyde (XXVI) exhibited signals at 7.83, 7.39, 4.44, and -0.2τ with relative intensities of 12:6:2:1. These peaks were assigned to the methyl groups on the two unsubstituted chelate rings, the methyl groups on the substituted ring, the two ring protons, and the aldehyde proton. The characteristic low field position of the last signal provided excellent evidence of the presence of an aldehyde group. The spectrum of the dialdehyde (XXVII) was almost identical, except for the expected changes in relative intensities to 6:12:1:2.

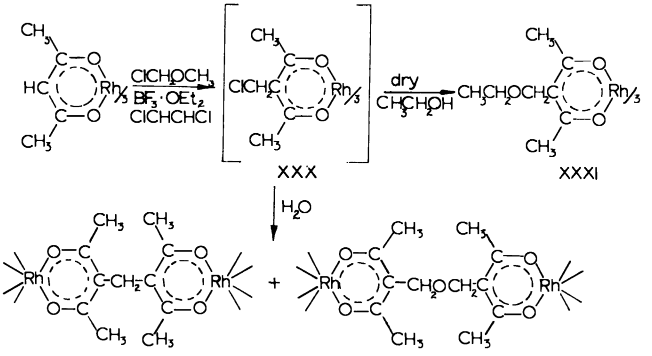
The substitution of the remaining acetylacetonate rings provided additional evidence of the assigned aldehyde chelate structures and opened the way for the preparation of a number of unsymmetrically substituted chelate rings.



M=Cr, Co
X=SCN, NO$_2$, Br, Cl

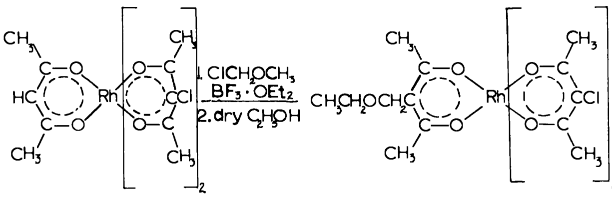
Chloromethylation of Chelate Ring

In the search for a reactive functional group which could be substituted on the acetylacetonate ring, chloromethylation of these chelates was attempted. The initially formed products were too reactive to be characterized directly. Treatment of rhodium acetylacetonate with chloromethyl methyl ether in the presence of boron trifluoride etherate afforded a solution of a very reactive species, apparently the chloromethyl chelate (XXX) (*26*). Hydrolytic workup of this intermediate yielded a polymeric mixture of rhodium chelates, but these did not contain chlorine! On the basis of evidence discussed later on electrophilic cleavage of carbon from metal chelate rings and on the basis of their NMR spectra, these polymers may be of the type shown below. Reaction of the intermediate with dry ethanol afforded an impure chelate which is apparently the trisethyl ether (XXXI). Treatment of the reactive intermediate with other nucleophiles gave intractable mixtures.



polymeric chelates

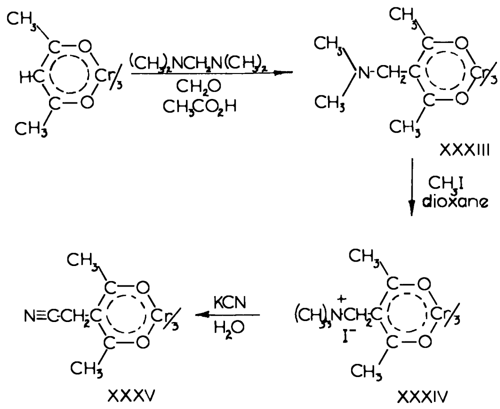
Our experience with the trischloromethyl rhodium chelate (XXX) and other polyfunctional chelates pointed out the difficulty in handling more than one reactive functional group in the same chelate molecule. We have learned to circumvent this problem by working with chelates in which there is only one reactive functional group and the other two chelate rings are substituted with inert groups. Thus reaction of the rhodium dichlorochelate (XXXII) with the chloromethylation reagent yielded an intermediate chloromethyl chelate, which could be converted into various derivatives in high yields. These reactions did not produce significant amounts of by-products and the desired products could be easily purified. Unfortunately, the unusual reactivity of the intermediate chloromethyl chelate precluded its isolation.



XXXII

Dimethylaminomethylation of Chelate Ring

The Mannich reaction is a particularly good method of introducing a reactive functional group into a sensitive aromatic nucleus. The reaction has been very useful in ferrocene chemistry. Treatment of chromium acetylacetonate under Mannich conditions yielded a tris-*N*,*N*-dimethylaminomethyl chelate (XXXIII). This remarkable substance was very difficult to purify because of its extreme solubility in all solvents ranging from *n*-heptane to water. The trisamino chelate (XXXIII) is a deep purple, hydroscopic oil and behaves like a typical organic amine. Reaction of this amine with methyl iodide afforded a trisquaternary ammonium salt (XXXIV), soluble in water but insoluble in organic solvents. When this salt (XXXIV) was treated with cyanide ion, trimethylamine was lost and the cyanomethyl chelate (XXXV) was formed.

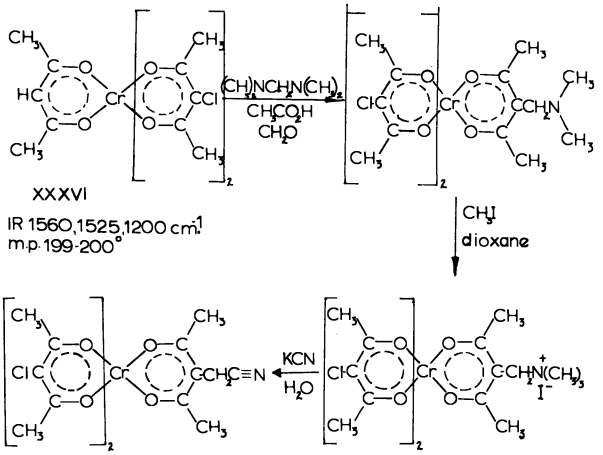


XXXIII

XXXIV

XXXV

The purification of chelates derived from the above scheme was tedious because of the trifunctionality of these substances and the corresponding possibility of mixtures of products. Again this problem was solved by studying this series of reactions on the dichlorochromium chelate (XXXVI), which has only one reactive ring.



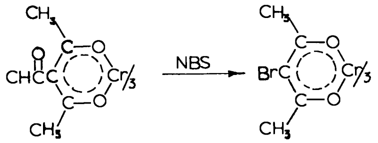
XXXVI

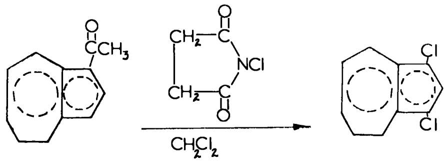
IR 1560,1525,1200 cm⁻¹
m.p. 199-200°

IR 2245,1565 cm⁻¹
m.p. 195-196.5°

Electrophilic Displacements from Chelate Ring

An example of the anomalous chemical properties often exhibited by functional groups on these chelate rings is the unusually facile displacement of several groups from these rings under electrophilic conditions. For instance, the acetylated chelates were found to react with *N*-bromosuccinimide in chloroform to yield the brominated chelates. The acetyl groups were also displaced from the chelate rings under nitration, chlorination, and thiocyanogenation conditions. The cleavage of carbon-carbon bonds under such mild electrophilic conditions has few classical analogies. A similar reaction is the reaction of 1-acetylazulene (XXXVII) with *N*-chlorosuccinimide to form dichloroazulene (*1*).

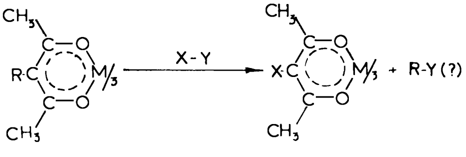




XXXVII

An extensive study of the electrophilic displacements from chelate rings has revealed a selectivity of leaving groups, of electrophiles, and of the metal in the chelate ring. For example, formyl groups are cleaved from the chelate ring much more slowly than acetyl groups, whereas carbethoxyl groups are not affected. On the other hand, dimethylaminomethyl groups are displaced more easily than protons. Cleavage of groups from substituted rhodium acetylacetonates proceeds much more slowly than from the corresponding chromium and cobalt chelates. These results are summarized in Table II.

TABLE II. Summary of Electrophilic Cleavage Reactions



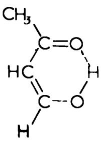
M	*R*	*X-Y Where Reaction Succeeds*	*X-Y Where Reaction Fails*
Cr, Co	CH_3CO	NBS, $Cu(NO_3)_2.3H_2O$ + Ac_2O NCS,[a] $(SCN)_2$,[a] Br_2 + $NaHCO_3$	NIS, HCl, ICl[b], Br_2[b]
Rh	CH_3CO	NBS[a]	$Cu(NO_3)_2.3H_2O$ + Ac_2O, NCS, HCl + $AlCl_3$
Cr, Co	CHO	....	NBS, $Cu(NO_3)_2.3H_2O$ + Ac_2O
Cr	C_2H_5OCO	....	NBS, $Cu(NO_3)_2.3H_2O$ + Ac_2O
Cr	$(CH_3)_2NCH_2$	NBS, NCS, $(SCN)_2$	$Cu(NO_3)_2.3H_2O$ + Ac_2O, Hg^{+2}, H_3O^+
Cr	Cl[c]	$Cu(NO_3)_2.3H_2O$	

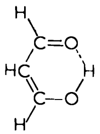
[a] Very slow reaction. [b] Much of chelate destroyed. [c] Dichlorochelate undergoes some cleavage.

Several peculiarities of these displacements are understandable in the light of the suggested electrophilic nature of the leaving groups. For instance, although the dimethylaminomethyl groups are easily cleaved under neutral electrophilic conditions, in the presence of strong acids little cleavage occurs. Furthermore, the quaternary ammonium salts are not attacked by electrophilic reagents. For similar reasons protons do not seem to cleave acetyl groups from these chelate rings.

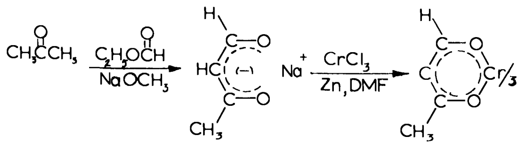
Syntheses and Reactions of Other Chelate Rings

Several of the unusual chemical properties of functional groups on metal acetylacetonate rings may be explained in terms of the considerable steric hindrance afforded the central carbon of the chelate ring by the flanking methyl groups. To examine this hypothesis the preparation of chelates of formyl acetone (XXXVIII) and malonaldehyde (XXXIX) was undertaken.

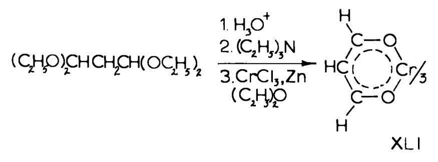

XXXVIII


XXXIX

Because of the sensitivity of formylacetone and malonaldehyde to self-condensation and to oxidation, the preparation of the slowly formed, inert metal chelates of these ligands is difficult. Furthermore, the powerful reducing power of these ligands seems to preclude the preparation of their cobalt(III) or rhodium(III) chelates, since these ions are good oxidizing agents. After a large number of unsuccessful experiments, a satisfactory method was developed for preparing the chromium(III) chelates of these ligands (*12*). This procedure involves the generation of a chromium(II)-chromium(III) equilibrium in the presence of a salt of the ligand in a donor solvent. Formylacetone was used as the sodium salt, whereas malonaldehyde was generated from its commercially available acetal and then converted into the triethylammonium salt.



XL



XLI

These new chelate systems were brominated, nitrated, and thiocyanogenated under conditions analogous to those previously described for the acetylacetonates. Chelates XL and XLI and their substitution products were found to be more easily degraded than the acetylacetonate, presumably because the oxygen donor atoms are less shielded from attack. The formylacetone chelate (XL) was separated into its diastereoisomeric cis and trans isomers by chromatography on alumina. The malonaldehyde chelate (XLI) represents the first authentic example of the parent of the 1,3-dicarbonyl ring systems.

Mechanism of Ring Substitution

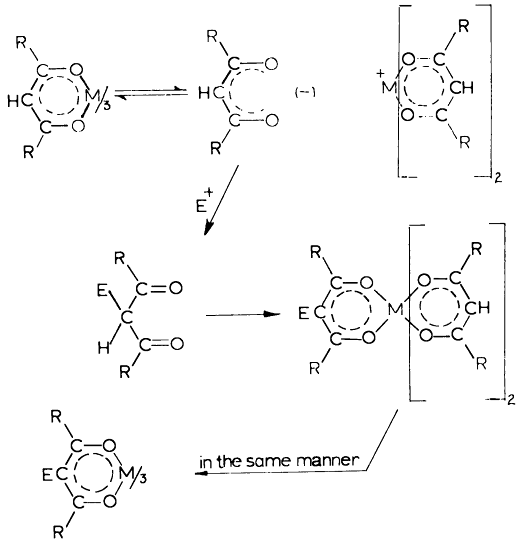
There appeared to be three limiting mechanistic paths through which electrophilic substitutions of the inert trisacetylacetonates could take place (*13*) (Figure 1).

A. Complete dissociation of an anionic bidentate ligand followed by reaction of the free ligand and subsequent recombination to form a substituted chelate ring.

B. Formation of an intermediate species with prior or subsequent breaking of one metal oxygen bond (probably to form a trigonal pyramid intermediate) followed by loss of a proton and reformation of the stable chelate ring.

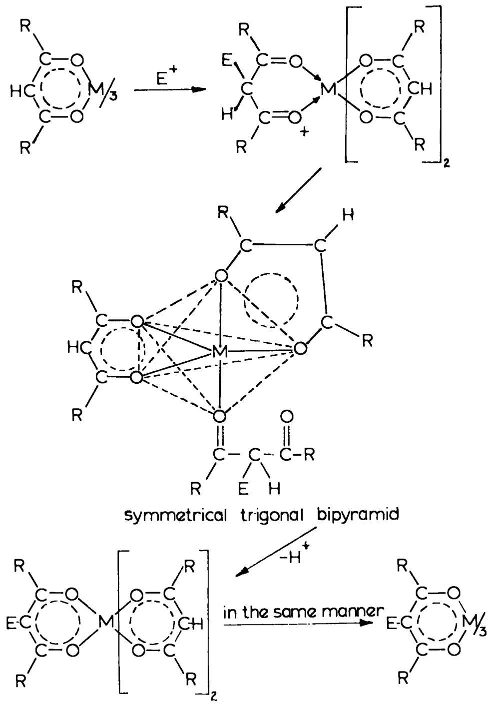
C. Reaction as a quasiaromatic system with the chelate ring remaining intact during a two-step reaction process.

Mechanism A

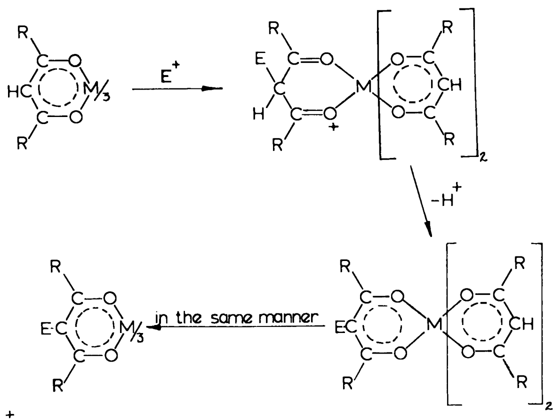


The work of Kluiber (*24*) eliminated mechanism A as a possibility in the bromination reactions. Kluiber demonstrated that there is no exchange between chromium(III) acetylacetonate and acetylacetone under conditions affecting ring bromination using *N*-bromosuccinimide. Using a variety of metal acetylacetonates and C^{14}-labeled acetylacetone, he performed tracer studies which showed that while some of the less stable chelates would exchange with the labeled diketone, the rate of exchange was not increased by performing the experiment under conditions of ring bromination with *N*-bromosuccinimide. Cobalt(III) and chromium (III) acetylacetonates showed negligible exchange under bromination conditions. These data are illustrated in Table III.

Mechanism B

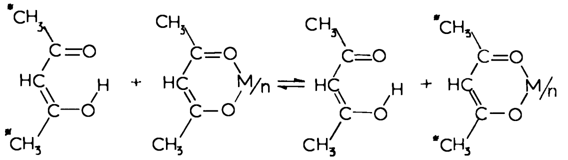


Mechanism C



E^+ = an electrophilic species

TABLE III. Per Cent Exchange of Metal Acetylacetonates with C^{14}-Labeled Acetylacetone



	$CHCl_3$	Dioxane	$CHCl_3/NBS$
Cu(II)	100	100	100
Mn(III)	100	...	...
Fe(III)	90	50	...
Be(II)	30	...	10
Al(III)	20	3	3
Cr(III)	1	...	1
Co(III)	0	...	...

It seemed likely that mechanism B would produce a symmetrical trigonal bipyramid and thus lead to racemization if an optically active substrate was used in the reaction. Mechanism A would certainly lead to total racemization, but mechanism C would not cause loss of optical activity. On the other hand it is possible to draw an asymmetric trigonal pyramid or an asymmetric tetragonal pyramid as a five-coordinate intermediate in mechanism B. The latter seem unlikely in organic solvents with weak donor properties. Furthermore, recent evidence suggests a symmetric trigonal pyramid as an intermediate in the racemization of trisacetylacetonate (*30*).

Therefore in an attempt to distinguish among mechanisms A, B, and C the acetylacetonates of chromium(III), cobalt(III), and rhodium(III) were partially resolved and the optically active chelates were then subjected to several electrophilic substitution reactions.

Since these trisacetylacetonates are nonionic and do not contain polar groups which would allow stoichiometric combination with an optically active resolving agent, unconventional methods must be applied to these resolutions. Three physical methods had been previously reported to effect meager partial resolution of these acetylacetonates. Moeller (*28*) carried out the partial resolution of these chelates by chromatographic adsorption on *d*-lactose hydrate columns, using benzene–petroleum ether as an eluent. In this manner Moeller had obtained samples of cobalt(III) acetylacetonate with molecular rotations up to −570° by using a 90-cm. column. Dwyer and Gyarfas (*20*) had effected partial resolution of cobalt(III) and chromium(III) acetylacetonates by adding *d*- or *l*-tris (ethylenediamine) cobalt(III) iodide to solutions of the acetylacetonates in ethanol and then salting out the acetylacetonates with ammonium chloride at 4°. These results were explained by the concept that the activities of the enantiomorphic forms of the asymmetric chelates were unequal in solutions containing an added optically active ion. Experiments by Kirschner (*23*) had confirmed the unequal activities of these enantiomorphic chelates in an asymmetric solution. Kirschner effected a partial resolution of cobalt(III) acetylacetonate by carrying out a zone melting operation on a frozen solution of the chelate and sodium (*d*)-dibenzoyltartrate in dioxane-water.

The chromatographic method of Moeller was chosen as the most convenient route to relatively large amounts of the partially resolved acetylacetonates. Two modifications of Moeller's technique made this a particularly powerful method of general application. It was found that all of the chelate passed through the lactose columns and thus these columns could be used over and over again without loss of effectiveness. Furthermore, longer columns gave a higher degree of resolution. A 16-foot column packed with 100-mesh *d*-lactose hydrate was highly effective yielding *l*-cobalt(III) acetylacetonate with molecular rotations as high as 4450°. Good resolution was also effected with the chromium and rhodium chelates. The optical activities were measured with a photoelectric polarimeter capable of making these measurements with a precision and reproducibility of better than 0.003°. The results of a typical experiment are illustrated in Table IV.

TABLE IV. Results of a Typical Chromatographic Resolution

Fraction Number	*Wt. of Solute in Fraction, Mg.*	*Wt. of Sample Used for Reading, Mg.*	*Observed Rotation*	*Molecular Rotation*
			Degrees	
1	6.68	6.68	−1.285	−4450
2	102.28	10.23	−0.430	−970
3	134.92	6.91	−0.075	−250
4	187.96	12.08	+0.059	+110
5	141.39	13.58	+0.400	+680
6	58.47	11.92	+0.253	+490
7	78.42	10.03	+0.136	+310

The three chelates were partially resolved on the 16-foot column, their optical activities measured accurately, and the asymmetric chelates subjected to the electrophilic substitution reactions. The optical activity of each product was then measured.

The results of these experiments are given in Table V. It is apparent from these data that the substitution reactions did not cause total racemization.

Since the optical purity of the starting materials and the molar rotations of the pure optically active products are unknown, it is not possible to assay any partial racemization. In most instances the molar rotation of the products is as large as or larger than the starting material. It is probable that no racemization took place in these reactions, but it is impossible to state this unequivocally without a knowledge of the relationship between the rotatory dispersion curves and visible spectra of the products and starting materials.

TABLE V. Asymmetric Chelates from Direct Substitution Reactions

Reaction Product	*Molecular Rotation*[a]		*Observed Rotation of Product, Degrees*
	Of starting material	*Of product*	
$[\mathrm{BrCAc_2}]_3\mathrm{Cr}$[b]	+363	+297	+0.092
$[\mathrm{BrCAc_2}]_3\mathrm{Co}$[c]	−765	−752	−0.150
	+514	+488	+0.080
$[\mathrm{BrCAc_2}]_3\mathrm{Rh}$	+20	+18	+0.038
$[\mathrm{O_2NCAc_2}]_3\mathrm{Cr}$	+390	+500	+0.016
$[\mathrm{O_2NCAc_2}]_3\mathrm{Co}$	−765	−388	−0.125
$[\mathrm{O_2NCAc_2}]_3\mathrm{Rh}$	−12	−26	−0.031
$[\mathrm{NCSCAc_2}]_3\mathrm{Co}$	−765	−858	−0.151
$[\mathrm{ICAc_2}]_3\mathrm{Cr}$	+363	362	+0.083
$[\mathrm{Ac_3C}][\mathrm{HCAc_2}]_2\mathrm{Rh}$	+22	+56	+0.033

[a] Specific rotation × molecular weight ÷ 100.
[b] Chromium and rhodium complexes measured at sodium line 589.3 mμ.
[c] Cobalt complexes measured at mercury line 546.1 mμ.

It is concluded that mechanism B is unlikely, since no total racemization was found in the reactions of chromium(III) and cobalt(III) acetylacetonates with a variety of electrophiles, and that these reactions occur in the same manner as in an aromatic system.

A more satisfactory solution to the mechanism of these substitutions now seems experimentally feasible. It is likely that the trisamino chelate (XXXIII) could be completely resolved by salt formation with a suitable optically active acid. The optically pure amine could then be converted by electrophilic cleavage into optically active bromo-, chloro-, and thiocyanate-substituted chelates. It would thus be a simple matter to determine whether these substitutions proceed with complete retention of asymmetry. Further, the question of a symmetrical five-coordinate intermediate in racemization of such compounds could probably be elucidated by a study of solvent polarity or salt effects on the kinetics of the racemization of these chelates.

Optical Properties of Cobalt Acetylacetonate

The partially resolved cobalt acetylacetonate was found to be optically stable in solution or in the solid state for long periods. However, slow crystallization of this substance always produced racemic crystals (*14*). Several of the optically active substituted cobalt chelates exhibited the same strange phenomenon. Removal of the solvent from solutions of optically active cobalt acetylacetonate with a slow stream of air yielded a solid which showed little apparent crystalline character under a polarizing microscope but dissolved to form a solution of about the same specific rotation as the starting solution.

Careful stepwise crystallization of cobalt acetylacetonate from solutions of the partially resolved chelate produced surprising results (*14*). A typical experiment is summarized in Table VI. The molecular rotation of the filtrates steadily increased as each crystal crop was removed until no solute remained in solution—at this time all optical activity had, of course, been lost. All crystal crops were racemic! It seems that the racemate is being preferentially crystallized from solution and at the same time a surface racemization is taking place to make up the deficient enantiomorph as the *d*, *l* crystals are formed.

TABLE VI. Recrystallization of Optically Active Cobalt(III) Acetylacetonate

Mother Liquor after Crystal Crop Removed	*Molecular Rotation of Solution at Mercury Line*	*Time, Hours*
Starting solution	−490	Zero
First crystallization	−720	18
Second	−730	24
Third	−950	48
Fourth	−1,500	72
Fifth	No sample left	120

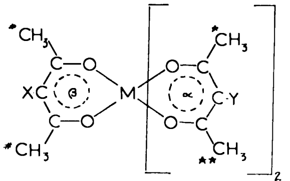
All crystal crops showed no optical activity.

Nuclear Magnetic Resonance Spectra of Mixed-Ring Chelates

The proton magnetic resonance spectra of the diamagnetic, mixed-ring chelates of rhodium(III) and cobalt(III) revealed an unexpected phenomenon which may have significant implications concerning the question of aromaticity in these compounds. The NMR data in Table I show that each functional group on the central carbon of the chelate rings produces a characteristic change in the chemical shift of the adjacent methyl groups in that chelate ring. These changes in chemical shift probably are caused by complex combinations of electronegativity and group anisotropy effects. The chemical shift data along with the integrated intensities of the various peaks permit an unequivocal assignment of each methyl signal in the spectra of the mixed-ring chelates. However, the NMR spectra of the mixed-ring chelates show another, unanticipated effect (*15*).

Consider the NMR spectra of a series of mixed-ring chelates in which two of the acetylacetonate rings are substituted differently from the third (Table VII). The methyl groups on the two like-substituted rings (type α) give rise to two symmetrical signals separated by a few cycles, but the methyl groups on the uniquely substituted ring (type β) exhibit only a single sharp peak. This splitting of the α-ring methyls is obviously not a spin-coupling effect, since no other splitting occurs in the spectrum.

TABLE VII. Proton Magnetic Resonance Spectra of Mixed-Ring Chelates



II

X	*Y*	*M*	*Solvent*[a]	*#CH_3*	NMR Signals in τ^b **CH_3*	 ***CH_3*	 $\Delta\gamma^c$
Cl	H	Rh	CCl_4	7.62	7.88	7.90	1.3
H	Cl	Rh	CCl_4	7.87	7.61	7.59	1.4
CH_3CO	H	Rh	$CHCl_3$	7.82	7.84	7.85	1.0
H	CH_3CO	Rh	$CHCl_3$	7.84	7.80	7.82	1.1
$CH_3CH_2CH_2CO$	H	Rh	$CHCl_3$	7.85	7.87	7.88	0.7
C_6H_5CO	H	Rh	$CHCl_3$	7.75	7.82	7.97	8.8
H	C_6H_5CO	Rh	$CHCl_3$	7.94	7.72	7.86	8.6
$CH_2OCH_2CH_3$	Cl	Rh	CCl_4	7.69	7.60	7.62	1.2
H	CHO	Co	$CHCl_3$	7.80	7.36	7.37	1.1
CHO	SCN	Co	$CHCl_3$	7.34	7.48	7.50	1.2
Cl	NO_2	Co	C_6H_6	7.53	7.48	. .	0
H	CH_3CO	Co	$CHCl_3$	7.79	7.71	7.73	1.8

[a] Chemical shift values dependent on nature of solvent.

[b] Other aspects of these spectra were compatible with assigned structures. All integrated intensities agree with proposed structures. No spin coupling detected in any instance.

[c] Separation between methyl signals of α rings in c.p.s. at 60 Mc. Confidence limits ±0.3 c.p.s.

A plausible explanation of the splitting of the methyl signals can be found in a long-range, intramolecular anisotropic shielding by the cyclic system of π electrons in the adjacent chelate rings. This splitting can be rationalized if one assumes that the chelate rings produce a long-range "ring current" anisotropy such as the strong effect characteristic of aromatic systems and furthermore that this "ring current" effect is perturbed by π-bonding substituents on the ring.

The two methyl groups on the β-ring are each held rigidly about 5 A. over the center of an α-ring. If the α-rings give rise to a long-range anisotropic shielding, each methyl group on the β-ring would experience a shielding from one of the α-rings. On the other hand, the two methyl groups on an α-ring differ, in that one is held over the axis of the β-ring, whereas the other is held over the second α-ring. If different substituents on the α and β rings cause unequal perturbations of the ring current magnetic anisotropy, then the shift between the α-ring methyl groups signals must reflect the difference between the α- and β-ring anisotropy.

This explanation is further supported by the fact that the chemical shift between the α-ring methyls is the same for each set of analogous mono- and disubstituted chelates—for example, mono- and diacetyl rhodium acetylacetonates. Furthermore, a chelate in which each of the three rings is differently substituted should exhibit six methyl signals in its NMR spectrum. Such a case has been observed. Finally, it seems reasonable that in certain cases two different substituents might have nearly equal perturbing effects on the ring current, so that the methyl groups on the α-type rings would show only a single peak. The mononitro dichloro cobalt acetylacetonate listed in Table VII is an example of this case (*16*).

If one assumes that only a closed cycle of unsaturation could give rise to this long-range magnetic anisotropy, data of this sort would lend credence to the possibility of aromaticity in these chelates. Obviously further experiments are necessary to test this hypothesis.

Summary

The chemistry of chelated ligands is a largely unexplored but potentially fruitful area of chemical research. Problems of significance to both inorganic and organic chemists may be found in this area. These results would seem to be a convincing argument for tearing down the traditional barrier between inorganic and organic chemistry. Finally, the diversity of techniques required to explore this field makes researches of this type particularly suitable vehicles for the training of graduate students.

Acknowledgment

The majority of the experimental work alluded to herein was carried out by the following students: Robert H. Barker, Robert P. Blair, Edmund T. Kittleman, Roger L. Marshall, and William L. Young, III.

Literature Cited

(1) Anderson, A. G., Nelson, J. A., Tazuma, J. J., *J. Am. Chem. Soc.* **75**, 4980 (1953).
(2) Bailar, J. C., Jr., Busch, D. H., "The Chemistry of Coordination Compounds," Reinhold, New York, 1956.
(3) Barnum, D. W., *J. Inorg. Nucl. Chem.* **21**, 221 (1961).
(4) Basolo, F., Pearson, R. G., "Mechanisms of Inorganic Reactions. A Study of Complexes in Solution," Wiley, New York, 1958.
(5) Beilstein, 4 Auflage, 3 Erganzungswerk, Band I, 3 Teil, system number 95, 3119 (1959).
(6) Calvin, M., Wilson, K. W., *J. Am. Chem. Soc.* **67**, 2003 (1945).
(7) Collman, J. P., Moss, R. A., Maltz, H., Heindel, C. C., *Ibid.*, **83**, 531 (1961).
(8) Collman, J. P., Moss, R. A., Goldby, S. D., Trahanovsky, W. S., *Chem. and Ind. (London)* **1960**, 1213.
(9) Collman, J. P., Young, W. L., III, *Inorg. Syn.* in press.
(10) Collman, J. P., Marshall, R. L., Young, W. L., III, Goldby, S. D., *J. Inorg. Chem.* **1**, 704 (1962).
(11) Collman, J. P., Abstracts of Papers, 141st Meeting, ACS, Washington, D. C., March 1962, p. 18M.
(12) Collman, J. P., Kittleman, E. T., *J. Am. Chem. Soc.*, **83**, 3529 (1961).
(13) Collman, J. P., and Blair, R. P., Abstracts of Papers, 140th Meeting ACS, Chicago, Ill., September 1961, p. 5N.

(14) Collman, J. P., Blair, R. P., Slade, A. L., Marshall, R. L., *Chem. and Ind. (London),* **1962,** 141.

(15) Collman, J. P., Marshall, R. L., Young, W. L., III, *Ibid.,* **1962,** 1380.

(16) Collman, J. P., Marshall, R. L., Young, W. L., III, Proceedings of Seventh International Conference on Coordination Chemistry, Stockholm, Sweden, June 1962, abstracts 55.

(17) Diehl, H., *Chem. Revs.* **21,** 39 (1937).

(18) Djordjevis, C., Lewis, J., Nyholm, R. S., *Chem. and Ind. (London)* **1959,** 122.

(19) Dryden, R. P., Winston, A., *J. Phys. Chem.* **62,** 635 (1958).

(20) Dwyer, F. P., Gyarfas, E. C., *Nature* **168,** 29 (1951).

(21) Fernelius, W. C., Bryant, B. E., *Inorg. Syn.* **5,** 105 (1957).

(22) Holm, R. H., Cotton, F. A., *J. Am. Chem. Soc.* **80,** 5658 (1958).

(23) Kirschner, S., Sonnessa, A. J., Bhatnagar, D. C., Moy, D., Abstracts of Papers, 138th Meeting, ACS, New York, September 1960, p. 14N.

(24) Kluiber, R. W., *J. Am. Chem. Soc.* **82,** 4839 (1960).

(25) *Ibid.,* **83,** 3030 (1961).

(26) Marshall, R. L., Ph.D. dissertation, University of North Carolina, 1962.

(27) Martell, A. E., Calvin, M., "Chemistry of Metal Chelate Compounds," Prentice Hall, New York, 1952.

(28) Moeller, T., Gulyas, E., *J. Inorg. Nucl. Chem.* **5,** 245 (1958).

(29) Nakamoto, K., McCarthy, P. J., Martell, A. E., *J. Am. Chem. Soc.* **83,** 1272 (1961).

(30) Piper, T. S., Seventh International Conference on Coordination Chemistry, Stockholm, Sweden, June 1962, and private communication.

(31) Reihlen, H., Illig, R., Wittig, R., *Ber.* **58B,** 12 (1925).

(32) Stallman, O., *J. Chem Educ.* **37,** 220 (1960).

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6

Syntheses and Reactions of Iron Isonitrile Complexes

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The syntheses of iron isonitrile complexes and the reactions of these complexes are reviewed. Nucleophilic reagents polymerize iron isonitrile complexes, displace the isonitrile ligand from the complex, or are alkylated by the complexes. Nitration, sulfonation, alkylation, and bromination of the aromatic rings in a benzyl isonitrile complex are very rapid and the substituent is introduced mainly in the para position. The cyano group in cyanopentakis(benzyl isonitrile)-iron(II) bromide exhibits a weak "trans" effect. With formaldehyde in sulfuric acid, benzyl isonitrile complexes yield polymeric compositions. One such composition contains an ethane linkage, suggesting dimerization of the transitory benzyl radicals. Measurements of the conductivities of benzyl isonitrile iron complexes indicate a wide range of ΔE (1.26 e.v.) and σ_0 (10^{23} ohm^{-1} cm.$^{-1}$) but no definite relationship between the reactivities of these complexes and their conductivities.

Two resonance structures may be written for the isonitrile (isocyanide) group:

$$\underset{\mathrm{A}}{\mathrm{R{:}\ddot{N}{::}C{:}}} \longleftrightarrow \underset{\mathrm{B}}{\mathrm{R{:}\overset{\oplus}{N}{:::}\overset{\ominus}{C}{:}}}$$

The abundant physical evidence on the molecular structure of isonitriles—namely, infrared and Raman spectra (*19*), nuclear magnetic resonance (*28*), electron diffraction studies (*9*), and dipole moment measurements (*36*)—indicates that the isonitrile group is best represented by the polar form, B. When coordinated to a metal, the isonitrile ligand acts as a donor, C, but also as an acceptor of electrons, D (*5*).

$$\underset{\mathrm{C}}{\mathrm{R\overset{\oplus}{N}{:::}C{:}\overset{\ominus}{M}}} \longleftrightarrow \underset{\mathrm{D}}{\mathrm{R{:}\ddot{N}{::}C{::}M}}$$

Hence, a very large number of isonitrile complexes of various metals with many different oxidation states (*30*) have been prepared (see Figure 1). In complexes with metals in low oxidation states the isonitrile ligand acts as an acceptor, D, as evidenced by the shift of the triple bond stretching mode toward lower wavelengths (Table I, 4 to 8). As the positive charge on the metal is increased, the ionic form of the isonitrile group, B, will be enhanced and the ligand will function mainly as a donor, C (Table I, 9 to 11). Metals (Zn, Cd, Hg) which coordinate with the isonitrile ligand mainly in the donor form, C, and which exhibit little π bonding between the metal and the ligand, form rather unstable complexes. Contrariwise, metals such as Ni and Cr which function as an electron donor in their zero valent states, form very stable isonitrile complexes.

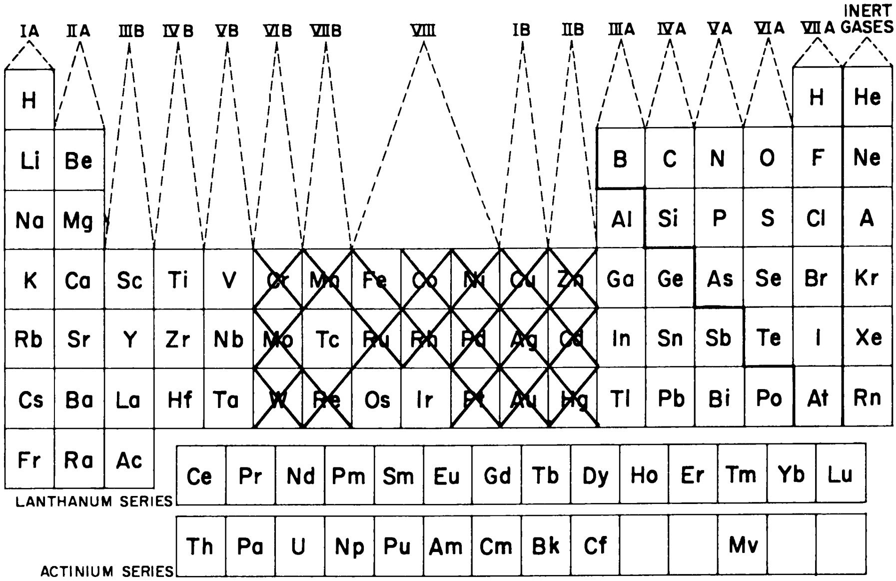
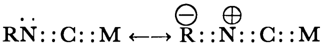


Figure 1. Summary of metals that form isonitrile complexes

The relative donor-acceptor properties of various isonitrile ligands can be estimated from the relative shift of the CN stretching band of the ligand in the mixed complexes. The shift of the CO stretching band to lower frequencies in mixed isonitrile-carbonyl complexes by 60 to 200 cm.$^{-1}$ (Table I, 12 to 15) indicates considerable π-bond formation between the metal and carbon monoxide. Hence, the carbon monoxide is a better electron acceptor than the isonitrile ligand in mixed carbonyl isonitrile complexes. In mixed isonitrile cyanide complexes—i.e., dicyanotetrakis(benzyl isonitrile) iron(II)—the frequency of the isonitrile band is increased by 34 cm.$^{-1}$ when compared to the noncoordinated ligand but it is increased by 77 cm.$^{-1}$ in the hexakis (benzyl isonitrile) iron(II) bromide complex; hence, the isonitrile group is a better electron acceptor than the cyanide group. On the other hand, little or no depression of the frequency of the isonitrile band occurs when the electron-donating property of the parasubstituent in phenyl isonitrile is varied, indicating relatively small contribution of resonance structure, E, in these compounds (Table I, 4 to 6)



$$\mathrm{R\ddot{N}::C::M} \longleftrightarrow \mathrm{\overset{\ominus}{R}::\overset{\oplus}{N}::C::M}$$

D E

Table I. Infrared Spectra of Isonitrile Complexes

No.	*Compound*	*CNR Stretching Frequency, Cm.* $^{-1}$	*Δν for CNR, Cm.* $^{-1}$	*CN or CO Stretching Frequency, Cm.* $^{-1}$	*Ref.*
1	Phenyl isonitrile	2136[a]			(*5*)
2	Methyl isonitrile	2142[a]			(*5*)
3	Benzyl isonitrile	2146[b]			(*37*)
4	$(C_6H_5NC)_4Ni^\circ$	2050, 1990[a]	(−) 86, 146		(*5*)
5	$(p\text{-}CH_3C_6H_4NC)_4Ni^\circ$	2065, 2033[a]			(*5*)
6	$(p\text{-}ClC_6H_4NC)_4Ni^\circ$	2049, 2008[a]			(*5*)
7	$(C_6H_5NC)_6Cr^\circ$	2070, 2012, 1965[a]	(−) 66, 124, 171		(*5*)
8	$(CH_3NC)_6Mn^{II}$	2129[c]	(−) 13		(*5*)
9	$(C_6H_5CH_2NC)_4Fe^{II}(CN)_2$	2180[a]	(+) 34	2092	(*12*)
10	$(C_6H_5CH_2NC)_5Fe^{II}CNBr$	2200[a]	(+) 54	2092	(*12*)
11	$(C_6H_5CH_2NC)_6Fe^{II}SO_4$	2223[a]	(+) 77		(*12*)
12	$(C_6H_5NC)Fe^\circ(CO)_4$	2165[a]	(+) 29	2054, 1994, 1970	(*5*)
13	$(CH_3NC)Fe^\circ(CO)_4$	2213[a]	(+) 71	2059, 1993, 1961	(*5*)
14	$(CH_3NC)_3Mo^\circ(CO)_3$	2186, 2150[c]	(+) 44, 8	1944, 1860	(*5*)
15	$(CH_3NC)_3Cr^\circ(CO)_3$	2185, 2147[c]	(+) 43, 5	1942, 1860	(*5*)

[a] *$CHCl_3$.*
[b] *Liquid.*
[c] *CH_2Cl_2.*

The problem of to what extent and how the reactivity of the isonitrile ligand is altered by coordination to a metal has an important bearing on the function of transition metals as homogeneous catalysts. It is also of interest from the standpoint of energy transfer in vivo, to determine whether or not there is any correlation between the reactivities of isonitrile complexes and their conductivities. In this paper we summarize some recent work on the syntheses and reactions of iron isonitrile complexes.

Syntheses of Iron Isonitrile Complexes

The first reported isonitrile complex was synthesized by the alkylation of silver ferrocyanide with ethyl iodide (*7*):

$$Ag_4Fe(CN)_6 + 4C_2H_5I \rightarrow (C_2H_5NC)_4Fe(CN)_2 + 4AgI \qquad (1)$$

A closely related synthesis is the alkylation of potassium ferrocyanide with dimethyl sulfate (*11*):

$$K_4Fe(CN)_6 + 3(CH_3O)_2SO_2 + H_2SO_4 \rightarrow [(CH_3NC)_6Fe](HSO_4)_2 + 2K_2SO_4 \qquad (2)$$

Another synthesis involves the esterification of hexacyanoferric(II) acid, a strong cyanic acid, with diazomethane (*31*):

$$H_4Fe(CN)_6 + 4CH_2N_2 \rightarrow (CH_3NC)_4Fe(CN)_2\ (\textit{cis, trans}) \qquad (3)$$

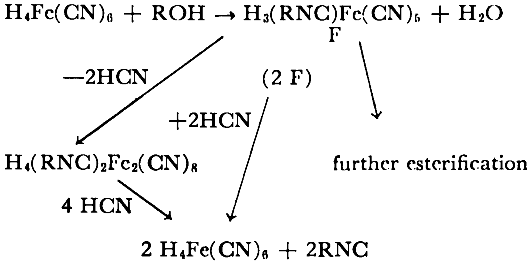
A general method for the preparation of iron isonitrile complexes is the addition of the isonitrile ligand to iron(II) perchlorate (*33*):

$$Fe(ClO_4)_2 + 4ArNC \rightarrow (ArNC)_4Fe(ClO_4)_2 \qquad (4)$$

and finally, mixed isonitrile carbonyl complexes are obtained when methyl isonitrile, for example, is added to iron pentacarbonyl (*20*):

$$Fe(CO)_5 + CH_3NC \rightarrow Fe(CO)_4(CNCH_3) \qquad (5)$$

In connection with our studies of the reactions of coordinated ligands, we have investigated several additional syntheses of iron isonitrile complexes.



Esterification of Hexacyanoferric(II) Acid. When hexacyanoferric(II) acid is heated with ethyl alcohol, esterification of the acid takes place (*15, 21*). The initial partially esterified hexacyanoferric(II) acid polymerizes with the evolution of hydrogen cyanide or is further esterified. Both reactions appear to take place concurrently. Addition of hydrogen cyanide to the reaction mixture causes liberation of ethyl isonitrile from the complex. Hence it is possible to synthesize isonitriles on a continuous basis—i.e., esterification of the strong hexacyanoferric(II) acid, replacement of the isonitrile in the complex by hydrogen cyanide, re-esterification, etc. (*15*). The over-all reaction is complex, and the precise course of the reaction has not been elucidated.

$$M_4Fe(CN)_6 + (4\text{–}8)\ RCH_2X \xrightarrow[100^\circ\ C.]{} \begin{array}{c} (RCH_2NC)_4Fe^{II}(CN)_2 \\ + \\ [(RCH_2NC)_5Fe^{II}CN]X \\ + \\ [(RCH_2NC)_6Fe^{II}]X_2 \end{array}$$

where M = Li, Na, $(CH_3)_4N$, K
X = Cl, Br, $OSO_2C_6H_4CH_3$ (*p*)
R = double bond
aromatic
heterocyclic

Alkylation of Alkali Metal Cyanides by Alkyl Halides Activated in the α-Position by a Double Bond. When a mixture consisting of 4 to 8 moles of an alkyl halide activated in the α-position by a double bond is heated with 1 mole of alkali metal ferrocyanide, several alkylation products of the ferrocyanide anion can be isolated from the reaction mixture (*12*). The relative proportions of the tetra-, penta-, and hexaalkylated complexes can be varied by varying the alkyl halide to ferrocyanide ratio and the time of reaction. When potassium ferrocyanide is alkylated with benzyl bromide at a ratio of 4 alkyl halides to ferrocyanide anion, short reaction times favor the tetraalkylated complex; an 8 to 1 ratio and long reaction times favor the hexaalkylated complex of the alkylating agents tested; benzyl bromide provided the fastest alkylation:

$$C_6H_5CH_2Br > C_6H_5CH_2OSO_2C_6H_4p\text{-}CH_3 > C_6H_5CH_2Cl \gg C_6H_5CH_2I$$

Benzyl bromide yields highest conversions to isonitrile complexes when M in $M_4Fe(CN)_6$ is potassium:

$$K > Na \cong (CH_3)_4N > Li$$

A typical reaction profile is summarized in Figure 2 for the reaction of potassium ferrocyanide with benzyl bromide. At the initial stages of the reaction the reaction mixture consists primarily of the tetra- and pentaalkylated complexes; when the maximum conversion of 92% to isonitrile complexes is reached, after 48 hours, the hexaalkylated product begins to appear.

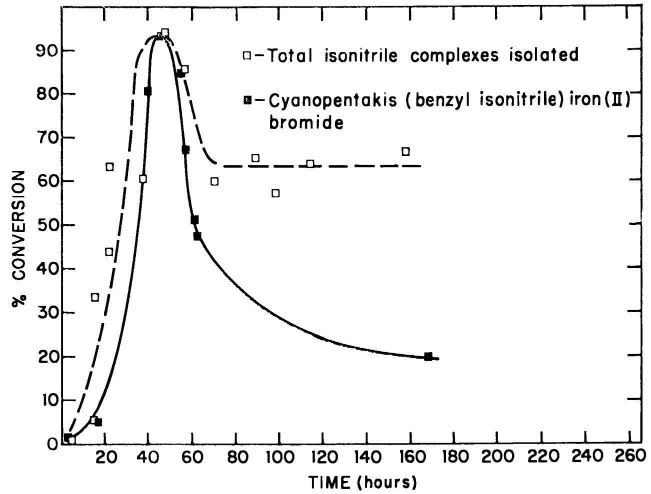
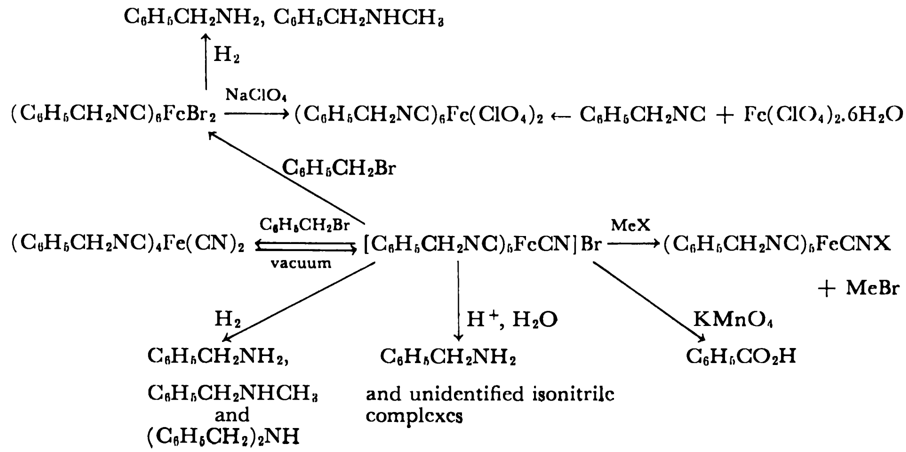


Figure 2. Reaction of potassium ferrocyanide with benzyl bromide

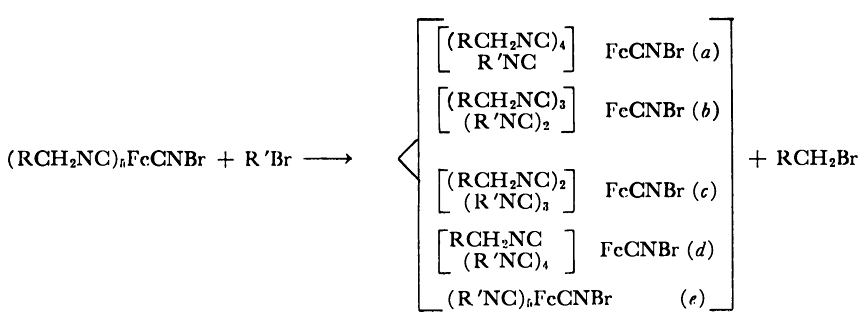
Cyanopentakis(benzyl isonitrile)iron(II) bromide, which represents a new class of iron isonitrile complexes, was investigated in some detail. This complex is diamagnetic and dissociates in nitrobenzene into two univalent-univalent ions as indicated by cryoscopic and conductivity measurements. It exhibits two peaks in the triple bond region of the infrared spectrum: one at 2200 cm.$^{-1}$ assigned to the isonitrile groups and another at 2092 cm.$^{-1}$ assigned to the cyano group. The structure proof of cyanopentakis(benzyl isonitrile)iron(II) bromide is:



Reduction of the complex on Raney nickel yielded benzylamine, *N*-methylbenzylamine, and *N,N*-dimethylbenzylamine but no β-phenylbenzylamine, a reduction product resulting under the same reaction conditions from benzyl cyanide. Hydrolysis with dilute sulfuric acid in acetic acid yielded benzylamine only, and oxidation of the complex with potassium permanganate gave 4.2 moles of benzoic acid per mole of complex. The bromide anion can be exchanged metathetically with various other anions such as perchlorate, iodide, and thiocyanate. When heated at 100° C. in vacuum, the complex lost one mole of benzyl bromide and yielded only one dicyanotetrakis(benzylisonitrile)iron(II) complex.

Further alkylation of cyanopentakis(benzyl isonitrile) iron(II) bromide gave the hexaalkylated product, which was prepared independently by a different route.

$$(RCH_2NC)_4Fe(CN)_2 \xrightleftharpoons{RCH_2Br} (RCH_2NC)_5FeCNBr \xrightleftharpoons{RCH_2Br} (RCH_2NC)_6FeBr_2$$



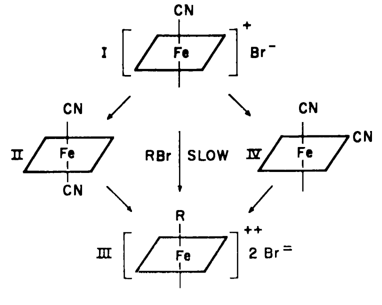
$$(RCH_2NC)_5FeCNBr + R'Br \longrightarrow \left\langle \left[\begin{array}{ll} \left[\begin{matrix}(RCH_2NC)_4\\ R'NC\end{matrix}\right] & FeCNBr\ (a)\\ \left[\begin{matrix}(RCH_2NC)_3\\ (R'NC)_2\end{matrix}\right] & FeCNBr\ (b)\\ \left[\begin{matrix}(RCH_2NC)_2\\ (R'NC)_3\end{matrix}\right] & FeCNBr\ (c)\\ \left[\begin{matrix}RCH_2NC\\ (R'NC)_4\end{matrix}\right] & FeCNBr\ (d)\\ (R'NC)_5FeCNBr & (e)\end{array}\right] \right. + RCH_2Br$$

Transalkylation Reaction. The alkylation reaction of potassium ferrocyanide with alkyl bromides activated at the α-carbon by a double bond (*14*) gave in each case good conversions to the corresponding isonitrile complexes. Since this method is limited to alkyl halides activated at the α-carbon by a double bond, it was of interest to develop a general method for the preparation of aliphatic isonitrile complexes.

It was found that the alkylation of dicyanotetrakis(benzyl isonitrile)iron(II) (I) to cyanopentakis(benzyl isonitrile)iron(II) bromide(II) and of cyanopentakis (benzyl isonitrile)iron(II) bromide to hexakis(benzyl isonitrile)iron(II) bromide (III) with benzyl bromide are equilibrium reactions.

When a foreign alkyl halide is introduced into the system, these alkylation reactions can be tailored into a synthesis of new isonitrile complexes by a transalkylation reaction. The transalkylation of isonitrile complexes can be accomplished with an alkyl halide, R'X, which is higher boiling than RBr, by a continuous distillation of RBr from the reaction mixture to yield *b*, *c*, *d*, and *e*. X in R'X can be Cl, Br, or I. RBr can be (*o*, *m*, *p*) $CH_3C_6H_4CH_2Br$, $C_6H_5COCH_2Br$, $CH_3(CH_2)_{14}CH_2Br$, $HO_2C(CH_2)_{10}CH_2Br$, etc. The reaction is general for the synthesis of aliphatic iron isonitrile complexes. The yields are usually good (50 to 80%), but the reaction products have been separated only by chromatography on alumina.

The mechanism of the transalkylation reaction is complex because of the many products involved and the possibility of internal rearrangement within the complex. The first step in the reaction may be the alkylation of I to III (Equation 6) or elimination of benzyl bromide to form II or IV. Since the transalkylation of II and III with *p*-nitrobenzyl bromide is slower than the total transalkylation of I with the same agent, I → IV seems to be the slow step in the reaction.



(6)

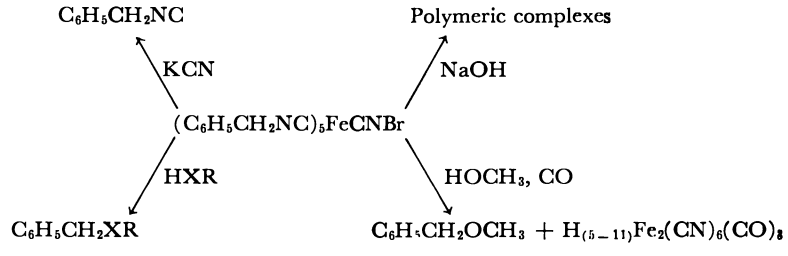
Unfortunately, it has been possible to isolate only one stereoisomer of dicyanotetrakis(benzyl isonitrile)iron(II), melting point 229–30° C. This complex was assigned the trans structure on the basis of the following evidence:

The complex is thermally stable when heated to 220° C.; no other isomer could be isolated. The nuclear magnetic resonance spectrum [in deuterochloroform, internally referenced to $(CH_3)_4Si$] shows only a singlet for the methylene group absorption at 5.20 τ, accounting for four methylene groups (*18*). If the compound were the "cis" structure, one should observe two different methylene bands in equal proportions in the nuclear magnetic resonance spectrum. Cyanopentakis(benzyl isonitrile)iron(II) bromide (and various other pentaalkylated complexes) shows a split methylene group in the NMR spectrum at 5.08 and 4.82 τ in a ratio of 4 to 1, the methylene group "trans" to the cyanide group being shifted by 0.26 τ downfield as compared to the noncomplexed benzyl isonitrile ligand. The infrared spectrum taken with either sodium chloride or calcium fluoride optics shows no splitting of the isonitrile band. Unfortunately, all attempts to measure the dipole moment of I were unsuccessful because of the insolubility of this compound in nonpolar solvents.

Reactions and Reactivities of Benzyl Isonitrile Iron(II) Complexes

It was considered of interest to see how the reactions of benzyl isonitrile, a model ligand, are modified by its coordination to iron and to determine whether other ligands in the octahedral complex influence the reactivity of the benzyl isonitrile group.

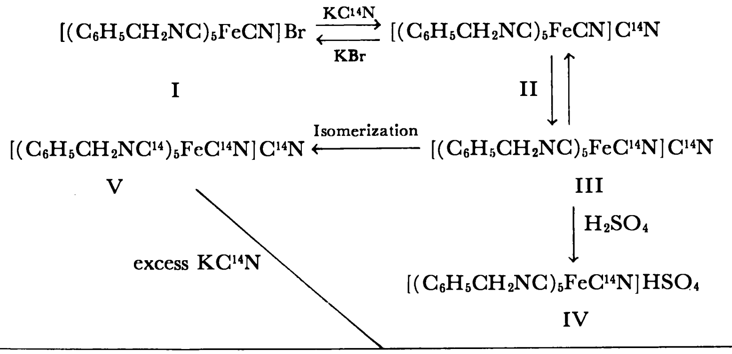
Two types of reactions were investigated: nucleophilic reactions and electrophilic reactions.



HXR = $HOCH_3$, HNH_2, $HSCH_2CH_3$, $HOCOCH_3$

Reaction of Cyanopentakis(benzyl Isonitrile)Iron(II) Bromide with Nucleophiles. Strong bases such as sodium hydroxide polymerize and/or decompose cyanopentakis(benzyl isonitrile)iron(II) bromide (compound II) to unidentified polymers (*13*). The products still show strong isonitrile bands in the infrared at 2180 and 2128 cm.$^{-1}$. When heated in a nitrogen atmosphere at 700 atm. and 150° C., the complex functions as an alkylating agent for various nucleophiles such as alcohols, amines, and acids. Highly colored, generally bluish, inorganic residues were formed in this reaction. When the nitrogen was replaced by carbon monoxide, a new, apparently polymeric, carbonyl cyanide complex was isolated. This complex is a strong acid containing 1.5 active hydrogens per formula weight. The infrared spectrum shows three peaks in the triple bond region: 2220, 2105, and 2030 cm.$^{-1}$. Slowly, upon standing in light, the initially white complex became blue. Unfortunately, the relative insolubility of this carbonyl cyanide complex (it is soluble only in sodium hydroxide and in concentrated sulfuric acid, in the latter with evolution of gas) has thus far prevented its structural determination.

On the other hand, the cyanide ion can react as a strong nucleophile on both the carbon and the iron atoms, liberating benzyl isonitrile. The reaction of potassium cyanide with II was investigated in some detail (Equation 7).



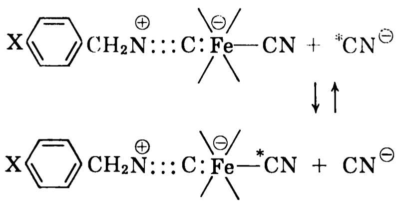
(7)

	$C_6H_5CH_2$-NC^{14}	$C_6H_5CH_2$-$NHC^{14}OH$	Benzyl Isonitrile Polymer	Iron Isonitrile Complexes	Inorganic Cyanides and Complexes
Conversion	~12.8%	~11.0%	18.3%	10.8 g.	16.8 g.
% radioactivity	6.0	2.0	55.5(?)	11.7	24.8

Label distribution on all carbons in III to V as indicated is partial.

When labeled potassium cyanide reacted with the complex in an aqueous methanol solution, the bromide was rapidly replaced and the labeled cyanide ion entered slowly into the coordination complex. When the reaction was conducted at higher temperatures in ethylene glycol dimethyl ether as the solvent, the label was distributed among the benzyl isonitrile, benzyl formamide, and the polymer resulting from benzyl isonitrile and the iron isonitrile complexes.

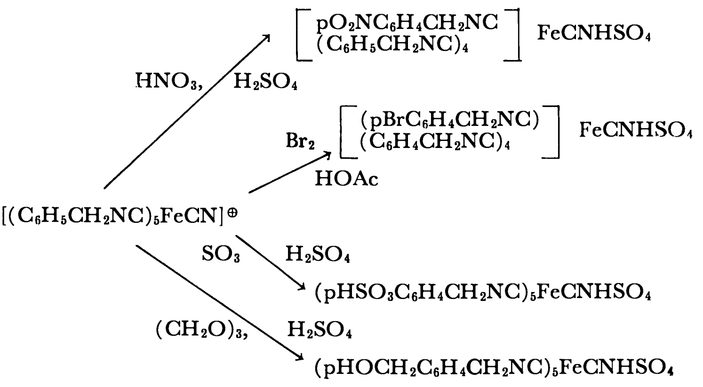
In a simple displacement of benzyl isonitrile by K^{14}CN from II, all the labeled atoms should appear in the isonitrile complex and none in the benzyl isonitrile. But the label was present in all of the products isolated and in each to a different extent. For example, the benzyl isonitrile was more radioactive than the *N*-benzyl formamide which must have been formed by addition of water to benzyl isonitrile. The results indicate that the internal isomerization (III → V, Equation 7), the generation of benzyl isonitrile and *N*-benzyl formamide, and the polymerization of benzyl isonitrile are concomitant reactions.



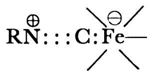
The exchange of labeled cyanide ion with II proceeds via either a penta- or a hepta-coordinated transition state complex as found for other cyanide complexes (*1*, *29*). The latter hypothesis is favored, since preliminary results indicate that an electron-withdrawing substituent, X, in $[(p\text{-}XC_6H_4CH_2NC)_5FeCN]HSO_4$, which apparently reduces the charge density of the iron, facilitates this exchange.

Electrophilic Reactions. The isonitrile group is best represented by the polar form, $R\overset{\oplus}{N}:::\overset{\ominus}{C}:$. Hence, the isonitrile is a strong nucleophile and base (*35*), and it hydrolyzes rapidly even in 0.1*N* acidic solutions. Dicyanotetrakis(benzyl isonitrile)iron(II) (compound I), cyanopentakis(benzyl isonitrile)iron(II) bromide (compound II), and hexakis(benzyl isonitrile)iron(II) bromide (compound III) are unusually acid-stable isonitrile complexes. No hydrolysis was observed in dilute acid and compound II could be hydrolyzed in 20 to 60% sulfuric acid with difficulty when heated for a prolonged time at 110° C. Therefore, complexes I, II, and III were ideally suited for the study of the reactions of the coordinated ligand with electrophiles in strongly acidic media.

Reaction of II with electrophilic agents, HNO_3, SO_3, and CH_2O in concentrated sulfuric acid, and with bromine in acetic acid, yielded the mono- or polysubstituted complexes, depending upon the reaction conditions (*16*). The position of substitution in these complexes was established by permanganate oxidation to the benzoic acids, esterification of the acids with diazomethane, and subsequent separation of the reaction products by vapor phase chromatography or by chromatography on alumina. The position of substitution was found to be predominantly or exclusively para; only when several rings in the same complex were substituted was it possible to isolate meta-substituted benzoic acids.



These findings are surprising, since the isonitrile ligand is best represented by the immonium form:



(see discussion above) which should be strongly meta-directing; Goss, Hanhart, and Ingold have found that nitration of trimethyl benzyl ammonium chloride yields 88% of the meta isomer and only 12% of the ortho-para isomers (*10*). Hammett's σ value for the $(CH_3)_3\overset{\oplus}{N}-$ group for the para position is (+) 0.859 compared to $\sigma = (+)\ 0.779$ for the $-NO_2$ group for the para position (*27*). Hence, the rate of nitration of the coordinated benzyl isonitrile group should be slower than the nitration of benzene by a factor of 10^2 to 10^3.

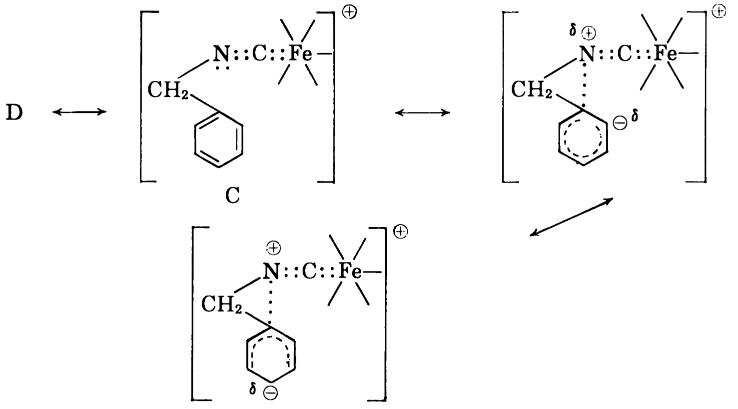
When 5 moles of benzene and 1 mole of II competed in concentrated sulfuric acid for the nitronium ion, the nitration of the first ring proceeded about 300 times faster than the nitration of benzene (Table II). Similarly the nitration of II proceeded about 150 times faster than that of toluene and comparable to that of *p*-chlorophenol.

Table II. Relative Reactivities of Isonitrile Complexes as Determined by Competition Method in Sulfuric Acid

(Expressed in moles of competing species per mole of complex, and relative distribution of nitro groups in competing species)

	Competing Species					
Complex	*C_6H_6*	*$C_6H_5CH_3$*	*pCl-C_6H_4OH*	*Complex I*	*Complex II*	*Complex III*
$(C_6H_5CH_2NC)_4$-$Fe(CN)_2$ (I)	(4 moles) 48					(1 mole) 2
$(C_6H_5CH_2NC)_5FeCN$-HSO_4 (II)	(5 moles) 300	(5 moles) 150	(1 mole) 1	(1 mole) 7.5		(1 mole) 19
$[(C_6H_5CH_2NC)_6Fe]_2$-SO_4 (III)	(6 moles) 0.4					

The foregoing results indicate that a powerful anchimeric rate-accelerating effect (*38*) must operate in the transition state of the electrophilic substitutions of II which exceeds the electron-withdrawing effect of the immonium form D in the mono-positive cation II:



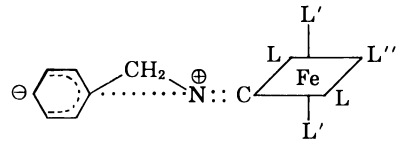
Closely analogous transition states in the solvolysis of β-chloroethylamines indicate that the anchimeric effect in these systems may accelerate the reaction rate by a factor of 10^3 to 10^4 as compared to the aliphatic halide in which the nitrogen is replaced by a carbon atom (*2, 4*).

A similar anchimeric rate-accelerating effect was observed for I and III (Table II). The infrared spectrum of I indicates that the isonitrile band is shifted by 34 cm.$^{-1}$ to higher frequencies and that of III by 77 cm.$^{-1}$. Hence in both complexes the isonitrile group is more ionic than in benzyl isonitrile and the same arguments should apply as to complex II.

Influence of the cis and trans Ligands in Octahedral Isonitrile Complex on the Reactivity of the Benzyl Group. The infrared spectra (Table I) of complexes I, II, and III indicate that the ionic form $R\overset{\oplus}{N}\equiv\overset{\ominus}{C}$ of the isonitrile group is most pronounced in III, less in II, and least in I.

It is now of interest to consider the electron-donor capabilities of the isonitrile ligand as influenced by the other ligands in the complex during electrophilic reactions.

Complexes I, II, and III may be represented by:



(8)

where L = $C_6H_5CH_2NC$, and L″, L′ = $C_6H_5CH_2NC$ or CN

The relative reactivities of I, II, and III as measured by competition for the nitronium ion ($NO_2^{\oplus}$) are summarized in Table II. These reactivity ratios (Table II) are necessarily smaller than the actual reactivity ratios. [Theoretically a large excess of the competing reagents should be employed in the competition method for establishing reactivities of two reagents (*23*); analytical difficulties thus far have prevented the more precise determination of reactivity of I, II, and III when employed in large excess with $NO_2^{\oplus}$.] As expected, the reactivity of III, which is a dipositive ion in sulfuric acid solution and in which the isonitrile ligand is most polarized, shows the least reactivity toward $NO_2^{\oplus}$ in competition with benzene. On the other hand, the reactivity of II toward $NO_2^{\oplus}$ in competition with benzene is approximately the same or slightly larger when compared to that of I; when the statistical factor is taken into account, the reactivity of II and I toward $NO_2^{\oplus}$ becomes 60 and 12, respectively, assuming that the reactivity of every aromatic ring in I or II is the same. A competitive reaction of I and II with $NO_2^{\oplus}$ and careful separation of the reaction products by chromatography revealed that II is more reactive than I toward $NO_2^{\oplus}$. Two possibilities for the reversal of reactivities, II > I, may be considered:

1. The cyanide groups (L″ = $C_6H_5CH_2NC$, L′ = CN) in I deactivate the aromatic ring(s) by a negative inductive effect.

2. The limiting form of the transition state in Equation 8 can form most easily if the Fe-C bond is strengthened by π bonding—i.e., donation of the Fe *d* electrons into the unoccupied *p*-orbitals of the isonitrile carbon.

Flow of electrons away from the iron will place a positive charge (effective) on Fe. The "trans" cyanide group in 8 (L′ = $C_6H_5CH_2NC$, L″ = CN) competes for the same set of orbitals and since it is a strong electron donor toward iron, it renders iron least positive and therefore enhances structure 8. Since the inductive effect is presumably small and since one aromatic ring in II appears more reactive toward NO_2 than the others, hypothesis 2 is the more probable one. A similar "trans" effect has been observed in carbon monoxide exchange in $Mn(CO)_5X$, where $X = Cl$, Br, or I (*39*).

As the electron-withdrawing power of the para-substituent in the benzyl isonitrile ligand increases, the effective charge on the iron atom decreases. The increase of the positive charge should facilitate an attack on the iron by strong nucleophiles, and indeed electron-withdrawing groups facilitate the cyanide exchange in II (see above). Electron-withdrawing groups also facilitate the exchange of the cyanide in the transalkylation reaction of isonitrile complexes of type II, where compounds such as $(p\text{-}O_2NC_6H_4CH_2NC)_5FeBr_2$ and $(C_6H_5COCH_2NC)_5FeBr_2$ were isolated.

Electron-withdrawing groups in the para position of the benzyl ligand should decrease the basicity of the cyanide nitrogen, if the cyanide group donates electrons to the iron atom. Indeed, the ease of alkylation of the partially alkylated ferrocyanide complexes—($K_3[RCH_2NCFe(CN)_5]$, $K_2[(RCH_2NC)_2Fe(CN)_4]$, etc.— is decreased as the electron-withdrawing power of the para-substituent group is increased:

$$(C_6H_5)_3CBr > (C_6H_5)_6CHBr > p\text{-}CH_3C_6H_4CH_2Br \cong o\text{-}CH_3C_6H_4CH_2Br > C_6H_5CH_2Br \cong CH_2{=}CH_2CH_2Br > p\text{-}ClC_6H_4CH_2Br > p\text{-}CH_3OCOC_6H_4CH_2Br \gg p\text{-}NO_2C_6H_4CH_2Br$$

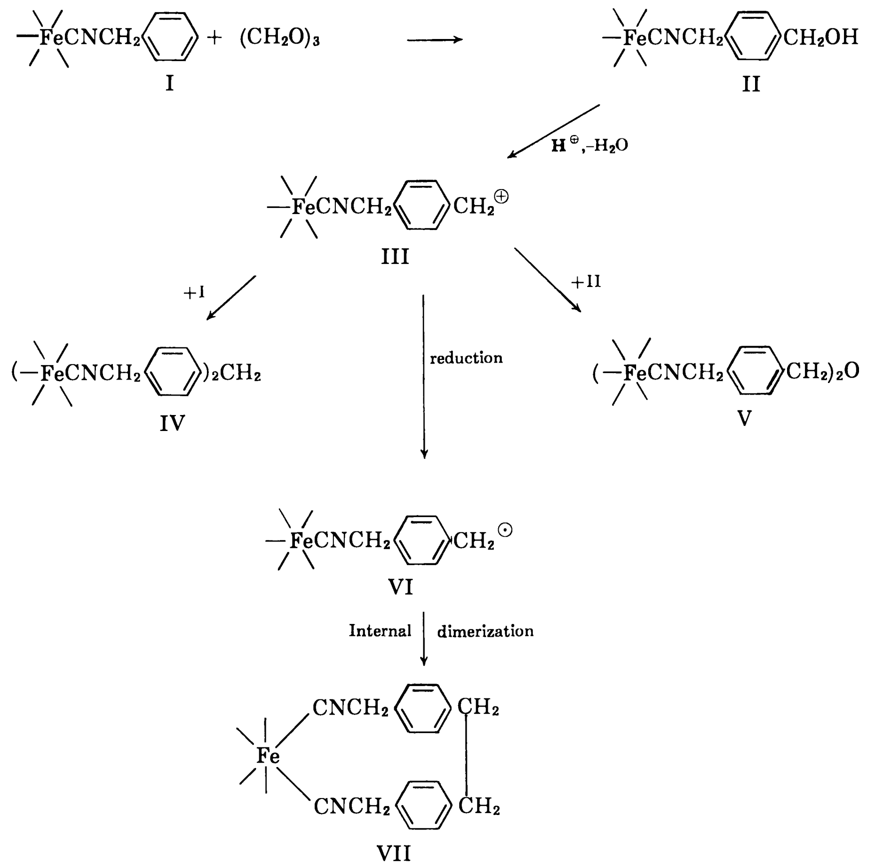
The rate of alkylation in the above sequence is actually dependent on the rate of dissociation of the alkyl halide *and* the nucleophilicity of the cyanide complex (*12*). The most stable carbonium ion derived from the alkyl halides in the above sequence—i.e., having the highest rate of dissociation—is the triphenylmethylcarbonium ion, which showed widely different rates of reaction with various cyanide complexes having widely different nucleophilicities toward crabon (*18*):

$$K_4Fe(CN)_6 > K_3Fe(CN)_6,\ K_3Co(CN)_6,\ K_2Ni(CN)_4,\ K_4Mo(CN)_8,\ K_4W(CN)_8 \gg K_3Mn(CN)_6,\ K_3Cr(CN)_6$$

Electron-Transfer Reactions

When paraformaldehyde is added to a solution of II in concentrated sulfuric acid at room temperature, a rapid reaction takes place, yielding colorless to orange polymeric compositions depending upon the ratio of reactants and the reaction condition employed (*17*). It is reasonable to assume that the polymerization of II with formaldehyde proceeds in a fashion similar to that of an activated aromatic ring with formaldehyde to yield as final products the diarylmethane and dimethylene oxy-derivatives, IV and V (Equation 9).

The structure of one of the orange polymeric compositions was investigated in some detail. The structure proof for this material is summarized below. When this composition was oxidized with sodium dichromate in sulfuric acid, a pentaketone was isolated in nearly quantitative yield. This pentaketone consumed 1.10 moles of periodic acid [a reagent employed for the quantitative oxidation of vicinal hydroxy or keto groups (*26*)] per formula weight and a dicarboxylic acid could be isolated from the reaction mixture. Hence the original polymeric composition must contain an ethane linkage. Formation of ethane linkages in the reaction of formaldehyde with an aromatic or pseudoaromatic system is known only for the reaction of ferrocene (*3*, *34*) with paraformaldehyde and in the polymerization of hydroxybenzyl alcohols at high temperatures (*22*). In both cases the intermediate benzylcarbonium ion (III, Equation 9) is reduced to the free radical,



which then dimerizes. Apparently the benzylcarbonium ion is reduced to the free radical by an electron transfer from the iron to the carbonium ion. It is thus far not clear how a second carbonium ion could be reduced within the same complex and the problem is now being investigated.

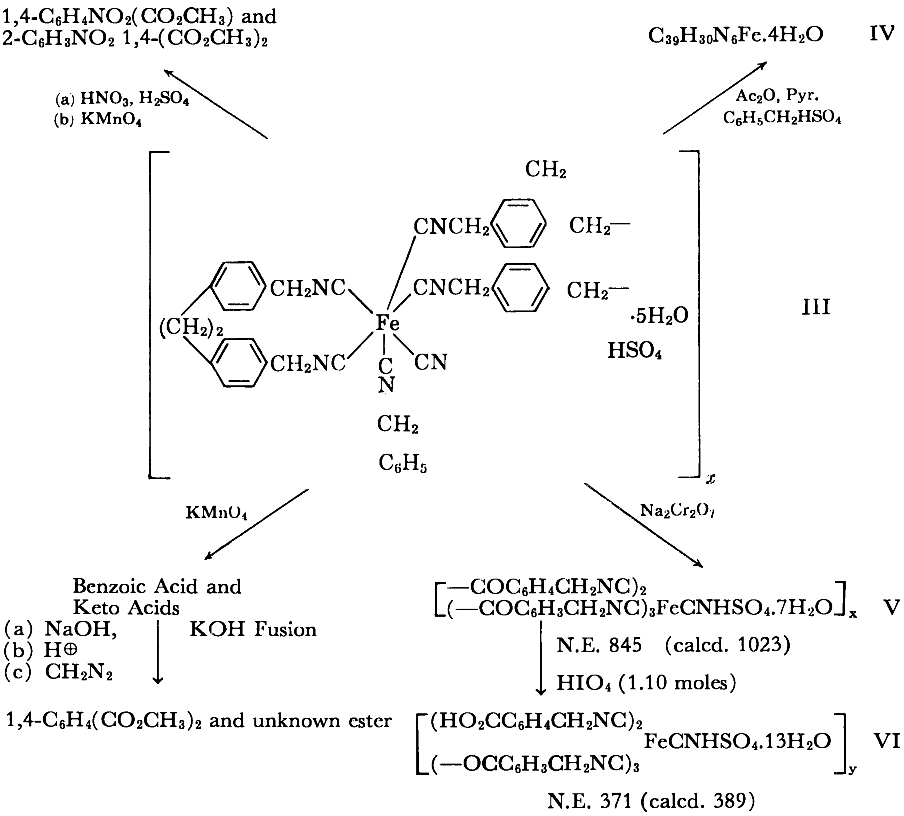
The facile reduction of the intermediate carbonium ion again indicates a considerable donation of the iron *d* electron to the unoccupied *p*-orbital of the isonitrile carbon. The rapid rate of reduction seems also to argue for a transition state or intermediate such as shown in Equation 8, which yields a conjugated system through which the electrons can be transferred rapidly.

Electrical Conductivities of Benzyl Isonitrile Iron(II) Complexes

In vivo the metal may assume two functions by virtue of complex formation: It may modify the reactivity of the coordinated ligand and it may influence the energy transfer between molecules. Hence, it was of interest to compare the reactivities and electron displacements in benzyl isonitrile iron(II) complexes in solution to their conductivities in the solid state.

Conductivity determinations were made on polycrystalline samples of the

Reactions and Structure Proof of $\left[\begin{matrix}(CH_2C_6H_3CH_2NC)_3\\(CH_2C_6H_4CH_2NC)_2FeCNHSO_4.5H_2O\end{matrix}\right]_x$



complexes following the experimental techniques of Inokuchi (25). The conductivity, σ, varied with temperature, T, in the following manner:

$$\log \sigma = \log \sigma_0 - \frac{\Delta E}{2.303\, kT} \tag{10}$$

where k = Boltzmann's constant, and σ_0 and ΔE are constants of the material.

Table III. Electrical Conductivities of Iron Isonitrile Complexes

	Complex	*σ at 25° C., Ohm^{-1} Cm.$^{-1}$*	*σ_0 at 25° C., Ohm^{-1} Cm.$^{-1}$*	*ΔE, E.V.*
1.	$(C_6H_5CH_2NC)_4Fe^{II}(CN)_2$	2.95×10^{-14}	6.4×10^{-8}	0.36
2.	$((C_6H_5)_2CHNC)_4Fe^{II}(CN)_2$	2.62×10^{-15}	2.4×10^{-7}	0.46
3.	$(C_6H_5CH_2NC)_5Fe^{II}CNBr$	4.76×10^{-13}	5.2×10^{15}	1.62
4.	$(C_6H_5CH_2NC)_5Fe^{II}CNHSO_4$	3.12×10^{-13}	1.9×10^{13}	1.53
5.	$(C_6H_5CH_2NC)_5Fe^{II}CNClO_4$	1.65×10^{-14}	5.0×10^{9}	1.39
6.	$(C_6H_5CH_2NC)_6Fe^{II}(ClO_4)_2$	2.78×10^{-14}	4.2×10^{4}	1.08

The experimental data for σ at 25° C., σ_0, and ΔE are summarized in Table III. As can be seen, all complexes are resistors at room temperature. Complexes of I, II, and III have widely different σ_0 and ΔE values. The conductivity of complexes of Type II approaches that of semiconductors at temperatures of about 100° C. ($\sigma = 10^{-5}$ ohm^{-1} cm.$^{-1}$).

When σ_0 is plotted *vs.* ΔE, a linear relationship is obtained (Figure 3). Polyacenes show a similar linear relationship, which may be parallel to that of the isonitrile complexes investigated and which is displaced toward lower values of σ_0. A comparison between the isonitrile complexes and polyacenes demonstrates most clearly the wide ranges of activation energies, ΔE, and of the constant, σ_0, which may be achieved merely in one series of coordination complexes as compared to polyacenes.

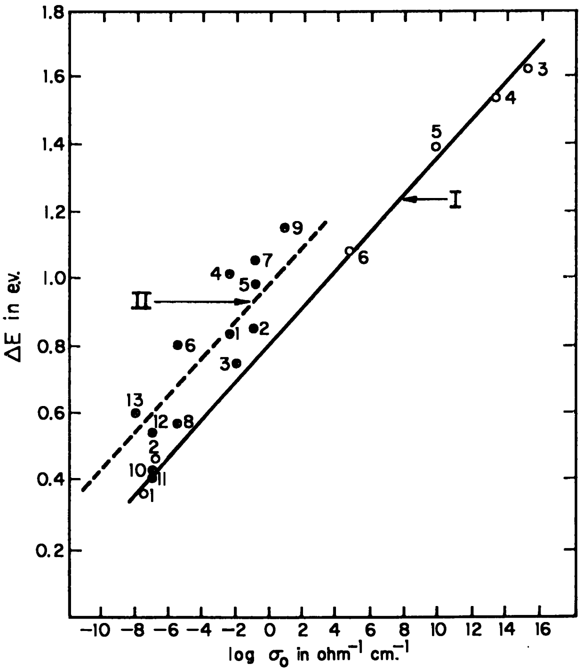


Figure 3. Linear relationship of ΔE vs. log σ_0 for iron isonitrile complexes (I) (○ referring to line I are listed in Table III) and of ΔE vs. log σ_0 for polyacenes (II), ● are:

1. *Anthracene (6)*
2. *Tetracene (32)*
3. *Pentacene (32)*
4. *Pyrene (32)*
5. *Perylene (32)*
6. *Anthranthrene (32)*
7. *Chrysene (32)*
8. *Ovalene (24)*
9. *Coronene (6)*
10. *Violanthrone (24)*
11. *Isoviolanthrone (24)*
12. *Pyranthrene (24)*
13. *meso-Naphthodianthrene (24)*

The activation energy, ΔE, of the isonitrile complexes is greatest for complexes of type I and smallest for complexes of type I. The reactivity of these complexes in solution toward the nitronium ion ($NO_2^{\oplus}$) was II > I > III. The different sequence of the activation energy for the conductivities as compared to the reactivities of these compounds can be understood in terms of the charge transfer model (Equation 11), which serves as a useful model for the description of the conducting process in organic crystals (*8*).

The charge transfer model for a donor molecule, A, and an acceptor molecule, B, may be described by Equation 11:

$$\Delta E = I_A - A_B - C \qquad (11)$$

where I_A is the ionization potential of A (equal to the energy of the highest occupied molecular orbital), A_B is the electron affinity of B (equal to the energy of its lowest unoccupied orbital), and C is a constant, relating to the distance the electron has to travel and the dielectric constant of the medium. The reactivity determination of various complexes in solution compares only to the nucleophilicities of these complexes, which are approximately equivalent to the ionization potentials in the charge transfer model; the electrophilicity, or approximately the electron affinity, of the attacking nitronium ion remains constant. On the other hand, the electron affinity in a crystal may determine the charge transfer process. The situation is most certainly even more complicated by the participation of the anion in the conducting process (see Table III).

Acknowledgment

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Literature Cited

(1) Adamson, A. W., Welker, J. P., Wright, W. B., *J. Am. Chem. Soc.* **73,** 4786 (1951)
(2) Bartlett, P. D., Ross, S. D., Swain, C. G., *Ibid.*, **69,** 2971 (1947); **71,** 1419 (1942).
(3) Berger, A., Kleinberg, J., McEwen, W. E., *Ibid.*, **83,** 2274 (1961).
(4) Cohen, B., van Artsdalen, E. R., Harris, J., *Ibid.*, **70,** 281 (1948); 74, 1875 (1952).
(5) Cotton, F. A., Zingales, F., *Ibid.*, **83,** 351 (1961).
(6) Eley, D. D., Parfitt, G. D., Perry, M. J., Taysum, D. H., *Trans. Faraday Soc.* **49,** 79 (1953).
(7) Freund, M., *Ber.* **21,** 931 (1888).
(8) Garrett, C. G. B., "Organic Semiconductors" in "Semiconductors," N. B. Hannay, ed., p. 634, Reinhold., New York, 1959.
(9) Gordy, W., Pauling, L., *J. Am. Chem. Soc.* **64,** 2952 (1942).
(10) Goss, F. R., Hanhart, W., Ingold, C. K., *J. Chem. Soc.* **1927,** 250.
(11) Hartley, E. G. J., Powell, H. M., *Ibid.*, **1933,** 101.
(12) Heldt, W. Z., *J. Inorg. Nucl. Chem.* **22,** 305 (1961).
(13) *Ibid.*, **24,** 73 (1962).
(14) *Ibid.*, p. 265.
(15) Heldt, W. Z., *J. Org. Chem.* **26,** 3226 (1961).
(16) *Ibid.*, **27,** 2604 (1962).
(17) *Ibid.*, p. 2608.
(18) Heldt, W. Z., unpublished results.
(19) Herzberg, G., "Molecular Spectra and Molecular Structure," Vol. II, "Infrared and Raman Spectra of Polyatomic Molecules," pp. 332–4, Van Nostrand, Princeton, N. J., 1959.
(20) Hieber, W., von Pigenot, D., *Ber.* **89,** 193 (1956).
(21) Hölzel, F., Krakora, J., *Monats.* **64,** 97 (1933–34).
(22) Hultzsch, K., *Z. angew. Chem.* **60A,** 179 (1948).
(23) Ingold, C. K., "Structure and Mechanism in Organic Chemistry," p. 245, Cornell University Press, Ithaca, N. Y., 1953.
(24) Inokuchi, H., *Bull. Chem. Soc. Japan* **24,** 222 (1951).
(25) Inokuchi, H., Akamatu, H., *Solid State Phys.* **12,** 93 (1961).
(26) Jackson, E. L., *Org. Reactions* **2,** 341 (1944).
(27) Jaffe, H. H., *Chem. Revs.* **53,** 191 (1953).
(28) Kuntz, I. D., Jr., Schleyer, P. von R., Allerhand, A., *J. Chem. Phys.* **35,** 1533 (1961).
(29) MacDiarmid, A. G., Hall, N. F., *J. Am. Chem. Soc.* **76,** 4222 (1954).
(30) Malatesta, L., *Progr. Inorg. Chem.* **1,** 283 (1959).
(31) Meyer, J., Domann, H., Mueller, W., *Z. anorg u. allgem. Chem.* **230,** 336 (1937).
(32) Northrop, D. C., Simpson, O., *Proc. Roy. Soc. (London)* **A234,** 124 (1956).
(33) Padoa, G., *Ann. Chim. (Rome)* **45,** 38 (1955).

(34) Rinehart, K. L., Jr., Michejda, C. J., Kittle, P. A., *Angew. Chem.* **72**, 38 (1960).
(35) Schleyer, P. von R., Allerhand, A., *J. Am. Chem. Soc.* **84**, 1322 (1962).
(36) Smyth, C. P., "Dielectric Behavior and Structure," pp. 249, 283, 317, 321, McGraw-Hill, New York, 1955.
(37) Ugi, I., Meyer, R., *Ber.* **93**, 239 (1960).
(38) Winstein, S., Lindegren, C. R., Marshall, H., Ingraham, L. L., *J. Am. Chem. Soc.* **75**, 147 (1953).
(39) Wojcicki, A., Basolo, F., *Ibid.*, **83**, 525 (1961).

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7

Effect of Coordination on the Reactivity of Aromatic Ligands

General Patterns of Reactivity

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The aromatic portion of a ligand will generally exhibit the same qualitative pattern for electrophilic substitution reactions, whether present in a coordination compound or not. The reactions of the extra-aromatic portion of such a ligand will usually show a pattern of reactivity similar to that of the free ligand but modified by the effects of masking and polarization which result from coordination. For heterocyclic ligands containing donor atoms integral with the aromatic systems, more profound changes may occur, but have been demonstrated only for the case of pyridine-*N*-oxide to date. When redox or autoxidation reactions are considered, coordination may result in very profound changes in the rates of these reactions. It is in this latter class of reaction that the most startling effects of coordination are to be seen.

At the present time the paucity of data renders it impossible to give a complete picture of the various ways in which coordination may affect the reactivity of aromatic ligands. It is possible to indicate the effects which the coordination process may have on the aromatic reactivity, however, to show how masking and polarization may affect reactivities, and to show at least a few instances where coordination may provide useful synthetic routes to some aromatic compounds.

While it may ultimately prove more fruitful to develop a completely independent method for predicting the reactions of coordinated ligands, at present the most promising approach is to see how the usual methods of theoretical organic chemistry can be used or modified to cover these cases. One of the most striking aspects of organic reactions (as compared with inorganic reactions) is the usual involvement of only a small portion of the molecule (functional group) and the way in which the different parts of the molecule preserve their typical reaction patterns as the gross structure of the molecule is subjected to changes. Put more directly, organic chemistry is built upon the assumption that a change in one portion of a molecule will usually have little or no effect on the qualitative aspects of reactivity of other portions, though it may affect the rates of these reactions. Thus we should expect a benzene ring in a coordination complex to show the same general properties as are found for benzene rings in typical organic compounds. Metal-arene complexes must be excepted from this statement and the discussion which follows.

For convenience, the reactions of aromatic ligands may be divided into three groups:

I. Reactions where the donor atom is external to the aromatic system

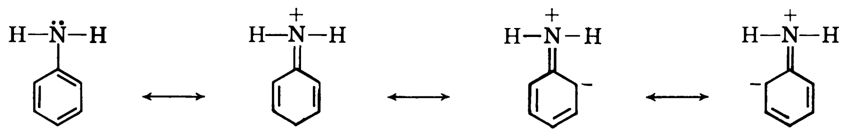
II. Reactions in which the aromatic system contains the donor atom as an integral part

III. Redox reactions in which the complex participates via changes involving both the ligand and central metal ion

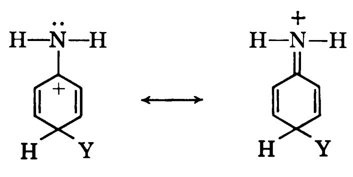
Aromatic Systems with an External Donor Atom

When the donor atom is a nitrogen or an oxygen atom adjacent to an aromatic system, the combination of the usual valence bond treatment of aromatic orientation for electrophilic reagents and the valence bond picture of the coordinate bond leads to the expectation that considerable changes in reactivity should occur. The chief reason for expecting that coordination will result in a change in the orientation of electrophilic attack upon anilines or phenols is the kind of canonical structure used to explain why the amino and hydroxy groups are ortho-para directing, rather than meta directing. If an electronegative atom such as nitrogen or oxygen is attached directly to a benzene ring, one might expect a pronounced deactivation toward typical electrophilic reagents and possibly even a meta-directing influence for such substituents. Thus the chloro and the fluoro groups are deactivating, while the nitro and sulfonic acid groups are meta directing. To explain the observed orientation pattern in both aniline and phenol it is customary to emphasize the importance of certain canonical forms which involve the sharing of the lone pair on the nitrogen or oxygen with the benzene ring. These may be used in the formulation of either the ground state (*54*) or the transition state (*48*). The resultant canonical forms which are assigned importance are shown below:

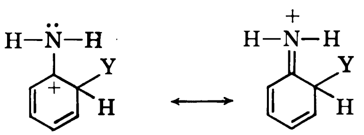
Ground State Formulation.



Transition State Formulation.



(three of these)
para attack by Y+



(three of these)
ortho attack by Y+

In either formulation the involvement of the lone pair in a coordinate bond would lead one to expect some obvious qualitative changes in reactivity. That such changes are not observed leads to the conclusion that the valence bond theory is somewhat inconsistent here. At present it seems that the valence bond picture of the coördinate bond is probably the culprit. In the crystal field treatment one would not expect the lone pair to be so deeply involved with the metal that it would be prevented from participation in such canonical forms as are necessary to explain the orientation. The difference between protonation and coordination is considerable, as protonation does lead to a change of orientation of aniline (*24*).

The crux of this difficulty is the charge distribution predicted by the theory. The use of a molecular orbital treatment is presumably capable of giving a more accurate picture of the charge redistribution which results from coordination. This whole problem is, however, still in a state of very rapid theoretical development (*55*).

All of the evidence at present available indicates that the aromatic portion of such ligands retains the same pattern of substitution with electrophilic reagents in the complex that it exhibited in the free state. This has been demonstrated with varying degrees of conclusiveness in the examples cited in Table I (*6, 12, 15, 16, 20, 26, 35–39, 41, 42, 46, 50, 57, 63, 73, 81*). No example of a change in orientation of such reactions has ever been confirmed, except for the peculiar case of tropolone. This compound undergoes an anomalous bromination with substitution occurring in the 3 position; other electrophilic reagents attack the 5 position initially. The copper complex, however, undergoes bromination at the 5 position, as would be expected for a normal electrophilic substitution. Further details on the anomalies of tropolone may be found in the literature (*6*).

Table I. Electrophilic Substitution Reactions of Aromatic Ligands

Ligand	*Metal Ion*	*Reaction*	*Orientation or Remarks*	*Lit.*
Aniline	Cr(III)	Bromination	*o,p*	(*73*)
Aniline, toluidines	Pd(II)	Bromination	*o,p*	(*26*)
Chromotropic acid	Ca(II)	Diazotization	*p* to —OH	(*37*)
m-Toluidine	Cu(II)	Chlorination	*o,p* to NH_2	(*16*)
Acetophenone	Al(III)	Bromination	*m*, coordination prevents side chain halogenation	(*57*)
Various phenols	Mg(II), Ca(II)	Diazotization	*p* to —OH	(*12, 15*)
8-Quinolinol	Cr(III), Fe(III), Cu(II), Al(III)	Bromination and chlorination	*o,p* to —OH	(*42*)
Salicylaldehyde	Co(III)	Bromination	*o,p* to —OH	(*81*)
Benzylisocyanide	Fe(II)	Various	*o,p* to —CH_2—N=C	(*20*)
Catechol	As(V)	Reimer-Tiemann	*o* to —OH	(*63*)
Catechol	As(V)	Bromination	*p* to —OH, rapid	(*41*)
Tropolone	Cu(II)	Bromination	5 position	(*6*)
Naphthalene derivatives	Cr(III), etc.	Sulfonation	Reversible reaction with complexes also	(*46*)
Salicylic acid	Al(III)	Nitrosation	*p* to —OH	(*38, 50*)
Catechol	Ga(III)	Diazotization	*p* to —OH	(*35, 36, 39*)

The results of these studies allow the behavior of the aromatic portion of a ligand to be predicted with some degree of confidence, if that of the free ligand is known or can be surmised. Coordination appears to have a small but definite effect on the nature of the transition state for electrophilic substitution (or its ease of attainment) when the donor atom is external to the aromatic system. The typical changes produced by coordination will be changes in the rates of reaction. From such meager evidence as is now available, these changes appear to be in the direction predicted on the basis of the polarization of the ligand by an adjacent positive charge.

When the ligand consists of both an aromatic system and reactive portions external to the aromatic system, the most interesting changes in reactivity occur in the latter portion of the molecule. These changes may be divided into two classes: masking of reactive groups and activation which results from the polarization arising from coordination.

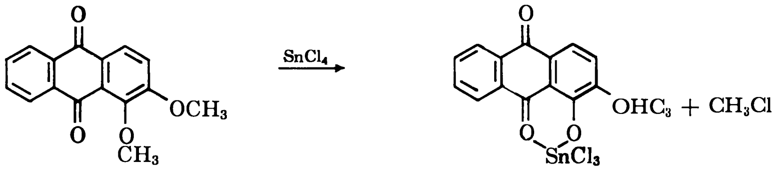
The masking effects are often striking. Both aliphatic and aromatic isonitriles are easily hydrolyzed and undergo a number of addition reactions at the —N═C linkage (*84*). The resistance of aliphatic isonitriles to hydrolysis is enormously increased by coordination, as was first clearly shown by Freund in 1888 (*14*, *19*, *45*). The resistance to addition reactions is shown in the recent elegant studies by Heldt (*20*) on coordination compounds containing benzyl isocyanide. Phenols are also rendered more resistant to oxidation by coordination (*12*, *15*, *37*), as is acetophenone to side chain halogenation (*57*), but some compounds are more readily reduced (*85*). This holds for complexes of metallic ions which are not readily oxidized or reduced. Studies involving reducible metal ions as coordination centers indicate that when the lower oxidation state is stabilized by coordination, a powerful catalysis of the oxidation process may occur (*8*, *40*, *64*, *79*). Masking effects of a very obvious sort seem not to be a general result of coordination and it is very difficult to determine when coordination will result in a masking effect, unless information on strictly analogous reactions is available.

It seems safe to say that coordination will generally decrease the reactivity of donor atoms in the first row of the periodic table through steric effects. With some reactions the extent of this steric hindrance may be small. Ammonia can be transformed into chloramines when coordinated (*34*), and aromatic acid chlorides coordinated to $AlCl_3$ or $TiCl_4$ may be esterified even when the functional group is a hindered one, as in mesitylene carbonyl chloride (*47*). These last reactions may proceed through a very reactive carbonium ion, whose existence is rendered possible by the polarization of the ligand which it suffers as a result of coordination.

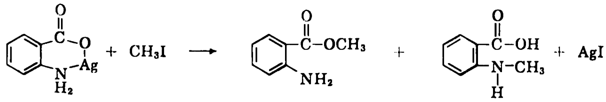
The coordination process may either stabilize or destabilize aromatic Schiff bases. If nickel(II) salts are added to ammoniacal solutions of salicylaldehyde, the precipitate obtained is the inner complex salt of nickel(II) and salicylaldimine (*61*). If beryllium chloride is added to the Schiff base derived from 2-hydroxy-1-naphthaldehyde and ethylamine, however, the Schiff base is decomposed and the inner complex of beryllium(II) and 2-hydroxy-1-naphthaldehyde is obtained (*59*). Here the strength of the coordinate bonds formed with the metal seems to determine which complex will be formed.

The number of cases where activation results from coordination is large and many examples have been collected by Hesse (*23*). The basis of the process is generally a very strong polarization, which results in a profound weakening of the other bonds of the donor atom. This was first recognized explicitly by Meerwein (*23*), who studied the increase in acidity of groups containing ionizable hydrogen when the atom to which the hydrogen is bonded forms a coordinate bond. Related reactions include the catalytic splitting of ethers via coordination to Mg(II), Zn(II) (*2*), or $SnCl_4$ (*60*):

$$MgI_2.2(C_2H_5)_2O + 2C_6H_5COCl \rightarrow 2C_2H_5I + 2C_6H_5COOC_2H_5 + MgCl_2$$



Another example which illustrates both the polarization and the freedom of reaction which is often found at the coordination site is (*29*):



In aromatic systems, the Lewis acids which activate via coordination are also capable of activating the aromatic system by the formation of σ and π complexes. There are a sufficient number of examples available to indicate that the activation via the latter processes is the more important of these, where all are present. Olivier (*52*) showed in 1913 that the kinetic behavior of such reactions consists of two portions. When the catalyst, say aluminum chloride, is present in less than the amount required to complex all the functional groups, the reaction is relatively slow and the catalytic activity is due to the small amount of Lewis acid resulting from the dissociation of the complex. As soon as all the functional groups are coordinated, any additional Lewis acid is found to accelerate the rate enormously. In these electrophilic substitutions it seems highly probable that the the activation involves the pi electron system of the benzene ring. Olivier studied the reaction sequence:

$$C_6H_4BrSO_2Cl + AlCl_3 \rightarrow C_6H_4BrSO_2Cl.AlCl_3$$

$$C_6H_4BrSO_2Cl.AlCl_3 + C_6H_6 \rightarrow C_6H_4BrSO_2C_6H_5.AlCl_3 + HCl$$

This type of duality of action is presumably present in other situations, such as the Fries rearrangement (*78*), the Friedel-Crafts reaction with acid chlorides (*65*) or acid anhydrides (*21*), and the catalytic chlorination of nitrobenzene (*17*). In these reactions it appears that the uncoordinated Lewis acid is the effective catalyst. The same situation is illustrated by recent work on aromatic amination (*32, 33*) and halogenation (*57, 58, 71*) and seems to be general feature of Lewis acid–catalyzed electrophilic reactions of aromatic compounds containing suitable donor groups.

When rearrangements occur in these systems, the products obtained will often be thermodynamically rather than kinetically determined (*62*). In some instances—e.g., the Gattermann-Koch reaction—the stability of the complex produced is responsible for the fact that the reaction can be carried out at all (*4, 9*).

Heterocyclic Systems with Internal Donor Atoms

When the donor atom is a part of the aromatic system, one would expect more obvious differences in reactivity. At present relatively little comparative information is available on such heterocyclic systems. Only on pyridine and its derivatives are there any reasonably extensive data. For pyridine a wide variety of coordination processes are available and pyridine-*N*-oxide as well as metallic complexes and complexes with nonmetallic Lewis acids must be considered. For comparative purposes the great reluctance with which pyridine undergoes electrophilic reactions is a considerable disadvantage. Protonation of the nitrogen is often cited as the cause of the slowness with which pyridine undergoes electrophilic substitutions in acidic media. When this is prevented by coordination to oxygen (*86*) or chromium(III) (*73*), or by the use of a sterically hindered derivative and a nonaqueous solvent (*3, 49*), the reactions are still sluggish unless the pyridine nucleus contains activating substituents. The general pattern of reactivity seems to be unchanged, however, for reactions other than nitration. It has been suggested by Daudel that the electronic densities and hence the reactivities of pyridine and the pyridinium ion will be very similar (*7*).

The preferred position for electrophilic substitution in the pyridine ring is the 3 position. Because of the sluggishness of the reactions of pyridine, these are often carried out at elevated temperatures, where a free radical mechanism may be operative. If these reactions are eliminated from consideration, substitution at the 3 position is found to be general for electrophilic reactions of coordinated pyridine, except for the nitration of pyridine-*N*-oxide (*30, 51*). The mercuration of pyridine with mercuric acetate proceeds via the coordination complex and gives the anticipated product with substitution in the 3 position (*72*). The bromination of pyridine-*N*-oxide in fuming sulfuric acid goes via a complex with sulfur trioxide and gives 3-bromopyridine-*N*-oxide as the chief product (*80*). In this case the coordination presumably deactivates the pyridine nucleus in the 2 and 4 positions. The bromination of this complex in fuming sulfuric acid proceeds more rapidly than the bromination of the pyridinium ion in 90% sulfuric acid. This behavior is reminiscent of those cases where the excess of Lewis base activates the aromatic system. The use of metallic halides in the catalytic halogenation of pyridine or pyridine derivatives leads to substitution in the 3 position or the 3 and 5 positions. The halides used include those of antimony, mercury (*5, 25*), and aluminum (*56*). The nucleophilic reactions of pyridine seem to be facilitated by coordination to a certain extent. Thus 3-bromopyridine is transformed to the corresponding amine derivative by treatment with an amine in the presence of cupric sulfate (*43*).

The mercuration of thiophene, which presumably goes by way of a coordination compound, gives an initial attack in the 2 position as expected from the reactions of thiophene itself (*67*). The bromination (or chlorination) of indazole or its silver salt also leads to the same products (*82*).

Redox Reactions

Redox reactions involving aromatic ligands may take unusual courses because of the ease with which electrons may be conducted through an aromatic system, though they need not do so. Thus the oxidation of free or coordinated 1,10-*o*-phenanthroline leads to 3,3′-dicarboxy-2,2′-bipyridine (*69*), and the oxidation of toluidine in sodium pentacyanotoluidine-ferrate(III) leads to phenazines (*22*) which can also be obtained by oxidation of the ligand itself (*10*).

The work of Fallab and his collaborators has shown how the coordination act may bring the reactants together in autoxidation reactions. In several instances coordination furnishes a catalytic path for these reactions. Specific examples include the autoxidation of Fe^{+2} in the presence of sulfosalicylic acid (*28*), the autoxidation of 1-hydrazinophthalazine by iron(II) (*27, 83*), and the autoxidation of a formazyl-zinc complex (*11*). It is probable that the importance of this kind of a mechanism will be more widely realized as more and more detailed kinetic studies are made on metal-catalyzed autoxidation reactions. Some other reactions which fall in this same category are the cuprous chloride–catalyzed oxidations of aromatic amines and related compounds which have been studied by Terentiev and his coworkers (*75*, *76*, *77*) and others (*31*, *53*). This field is a very large one and was early studied from the viewpoint of coordination chemistry (*68*).

Of the recent work involving aromatic ligands, that of Taube and Sebera is perhaps the most striking (*13*, *74*). They were able to demonstrate that an electron can be transferred from Cr(II) to Co(III) through a conjugated system involving the metals and terephthalic acid derivatives. This indicates possible synthetic applications of these reactions.

Theoretical Studies

The number of instances in which theoretical values of the electron densities (or equivalent information) at various atoms are available for both a ligand and its complexes are very few. Of the molecular orbital calculations on complexes which have been carried out, two are of direct interest. The study of pyridine and its complexes by Schlafer and Konig (*66*) showed that the π-π^* transition of the pyridine itself was only slightly affected by coordination. Transitions involving the transfer of electrons from the metal to the ligand ($t_{2g} \rightarrow \pi_1{}^*$ or $t_{2g} \rightarrow \pi_2{}^*$) are rendered possible by the coordination act, but the relevance of such transitions to the aromatic reactivity is not at all clear. The calculated values of electron densities of porphin and its iron complexes have been published by Spanjaard and Berthier (*70*). These show that the π-electron densities on the atoms of the porphin ring are only very slightly modified when porphin is changed to an ionic iron(II)-porphin complex. Related calculations have been carried out by Goudot (*18*) but are more concerned with bond-breaking processes than with the aromatic portion of catalysts such as catalase.

The above remarks apply to aromatic ligands. In general, the Lewis acid portion of a complex undergoes a much greater change upon coordination than the base (*1*) and coordination can change the orientation in compounds such as phenylboronic acid (*44*) and presumably other similar organometallic coordination centers.

Literature Cited

(1) Bauer, S. H., Adv. Chem. Ser., No. **32**, 89 (1961).
(2) Blaise, E. E., *Compt. rend.* **139**, 1211 (1904); **140**, 661 (1905).
(3) Brown, H. C., Kanner, B., *J. Am. Chem. Soc.* **75**, 3865 (1953).
(4) Campbell, H., Eley, D. D., *Nature* **154**, 85 (1944).
(5) Chemische Fabrik von Heyden, A. G., Swiss Patent **174,893**; *Chem. Zent.* **1935**, II, 2283.
(6) Cook, J. W., Gibb, A. R. M., Raphael, R. A., *J. Chem. Soc.* **1951**, 2244.
(7) Daudel, R., Lefebure, R., Moser, C., "Quantum Chemistry," p. 251, Interscience, New York, 1959.
(8) Denisov, E. T., Emanuel, N. N., *Russian Chem. Rev.*, No. **12**, 645 (1960).
(9) Dilke, M. H., Eley, D. D., *J. Chem. Soc.* **1949**, 2601.
(10) Elderfield, R. C., ed., "Heterocyclic Compounds," Vol. **6**, p. 637, Wiley, New York, 1957.
(11) Fallab, S., Erlenmeyer, H., *Helv. Chim. Acta* **42**, 1153 (1959).
(12) Farbwerke vorm. Meister, Lucius, und Brüning, German Patents **174,905,175,827, 177,624, 178,304, 188,819** (1904).
(13) Fraser, R. T. M., *Rev. Pure Appl. Chem.* **11**, 64 (1961).
(14) Freund, M., *Ber.* **21B**, 935 (1888).
(15) Friedländer, P. W., "Fortschritte der Teerfarbenfabriken und verwandte Industriezweige," Vol. **III**, pp. 612, 616, 619, 620, 1904.

(16) Genschev, M., Pojarliev, I., Kolev, D., *Compt. Rend. Acad. Bulgare Sci.* **12**, 305 (1959).
(17) Goldschmidt, H., Larsen, H., *Z. phys. Chem.* **48**, 424 (1904).
(18) Goudot, A., *Compt. rend.* **252**, 125 (1961); *Zhur. Fiz. Khim.* **34**, 2137 (1960).
(19) Hartley, E. G. J., *J. Chem. Soc.* **1910**, 1066; **1912**, 705; **1913**, 1196; *Proc. Chem. Soc.* **26**, 90 (1910); **28**, 101 (1912); **29**, 188 (1913).
(20) Heldt, W. Z., *J. Inorg. Nucl. Chem.* **22**, 305 (1961); "Advances in the Chemistry of the Coordination Compounds," S. Kirschner, ed., p. 321, Macmillan, New York, 1961.
(21) Heller, G., *Angew. Chem.* **19**, 669 (1906).
(22) Herington, E. F. G., "International Conference on Coordination Chemistry," London, April 6–11, 1959, Chemical Society, London, Spec. Pub. 13, p. 129, 1960.
(23) Hesse, G., "Katalyse durch Komplexbildung," in "Handbuch der Katalyse," Band VII, G. M. Schwab, ed., 2 Hälfte, pp. 68–108, Springer Verlag, Vienna, 1943; "Katalyse über komplexe Kationen und Anionen," in Houben-Weyl, "Methoden der Organischen Chemie," Bd. IV, T. 2, pp. 65–136, G. Thieme Verlag, Stuttgart, 1955.
(24) Holleman, A. F., *Chem. Revs.* **1**, 187 (1925).
(25) I. G. Farbenindustrie A. G., German Patent **595,461**, *Chem. Zent.* **1934**, II, 1029.
(26) Jetton, R. L., Jones, M. M., *Inorg. Chem.*, in press.
(27) Kaden, T., Fallab, S., in "Advances in the Chemistry of the Coordination Compounds," S. Kirschner, ed., p. 654, Macmillan, New York, 1961.
(28) Kaden, T., Walz, D., Fallab, S., *Helv. Chim. Acta* **43**, 1639 (1960).
(29) Karrer, P., Nageli, C., Weidmann, H., Wilbuschewich, L., *Ibid.*, **2**, 242 (1919).
(30) Katritzky, A., *Quart. Rev.* **10**, 395 (1956).
(31) Kinoshita, K., *Bull. Chem. Soc. Japan* **32**, 777, 780, 783 (1959).
(32) Kovacic, P., Bennett, R. P., *J. Am. Chem. Soc.* **83**, 221 (1961).
(33) Kovacic, P., Foote, J. L., *Ibid.*, **83**, 743 (1961).
(34) Kukushkin, Y. N., *Zhur. Neorg. Khim.* **2**, 2371 (1957); **4**, 2460 (1959); **5**, 1943 (1960).
(35) Kuznetsov, V. I., *J. Gen. Chem. USSR* **20**, 807 (1950).
(36) Kuznetsov, V. I., Nemodruk, A. A., *Ibid.*, **25**, 117 (1955).
(37) *Ibid.*, **26**, 3657 (1956) (Consultants Bureau trans.).
(38) *Ibid.*, **29**, 988 (1959) (Consultants Bureau trans.).
(39) Kuznetsov, V. I., Nemodruk, A. A., *Sb. Stateĭ Obshcheĭ Khim.* **2**, 1373 (1953).
(40) Langenbeck, W., Kasper, F., *Ber.* **89**, 2460 (1956).
(41) Larkins, T. H., Jr., Vanderbilt University, unpublished work, 1962.
(42) Maguire, K. D., Jones, M. M., *J. Am. Chem. Soc.*, in press.
(43) Maier-Bode, H., German Patent **586,879**; *Chem. Zent.* **1934**, II, 129.
(44) Mare, de la, P. B. D., Ridd, J. H., "Aromatic Substitution," p. 86, Butterworths, London, 1959.
(45) Meisenheimer, J., *Ber.* **58**, 13 (1925).
(46) Moll, F., Lange, F., German Patent **651,429** (1938).
(47) Mori, B., Gohring, J., Cassimatis, D., Susz, B. P., *Helv. Chim. Acta* **45**, 77 (1962).
(48) Morrison, R. T., Boyd, R. N., "Organic Chemistry," p. 296, Allyn and Bacon, Boston, 1959.
(49) Muller, N., Wallace, W. J., *J. Org. Chem.* **24**, 1151 (1959).
(50) Nemodruk, A. A., *J. Gen. Chem. USSR* **28**, 1051 (1958) (Consultants Bureau translation).
(51) Ochiai, E., *J. Org. Chem.* **18**, 534 (1953).
(52) Olivier, S. C. J., *Rec. trav. chim.* **33**, 92, 244 (1914); thesis, Delft, 1913.
(53) Paris, M., Williams, R. J. P., *Discussions Faraday Soc.*, No. **29**, 153 (1960).
(54) Pauling, L., "The Nature of the Chemical Bond," 3rd ed., p. 207, Cornell University Press, Ithaca, N. Y., 1960.
(55) Pearson, R. G., *Record Chem. Progr.* **23**, 53 (1962).
(56) Pearson, D. E., Hargrove, W. W., Chow, J. K. T., Suthers, B. R., *J. Org. Chem.* **26**, 789 (1961).
(57) Pearson, D. E., Pope, H. W., *Ibid.*, **21**, 381 (1956).
(58) Pearson, D. E., Pope, H. W., Hargrove, W. W., Stamper, W. E., *Ibid.*, **23**, 1412 (1958).
(59) Pesis, A. S., *Zhur. Neorg. Khim.* **6**, 1004 (1961).
(60) Pfeiffer, P., *Ann.* **398**, 141 (1913).
(61) Pfeiffer, P., Buchholz, E., Bauer, O., *J. prakt. Chem.* **129**, 163 (1931).
(62) Pitzer, K. S., Scott, D. W., *J. Am. Chem. Soc.* **65**, 812 (1943).
(63) Reihlen, H., Illig, R., Wittig, R., *Ber.* **58**, 12 (1925).
(64) Resnick, R., Cohen, T., Gernando, Q., *J. Am. Chem. Soc.* **83**, 3344 (1961).
(65) Ridell, W. A., Noller, C. R., *Ibid.*, **52**, 4365 (1930).
(66) Schlafer, H. L., Konig, E., *Z. phys. Chem.* **30**, 143 (1961).
(67) Shephard, A. F., Henne, A. L., Midgley, T., Jr., *J. Am. Chem. Soc.* **56**, 1355 (1934).

(68) Shibata, K., Shibata, Y., "Katalytische Wirkungen der Metallkomplexverbindungen," Iwata Institute of Plant Biochemistry, Tokyo, 1936.
(69) Smith, G. F., Richter, F. P., "Phenanthroline and Substituted Phenanthroline Indicators," pp. 20–1, G. F. Smith Chemical Co., Columbus, Ohio, 1944.
(70) Spanjaard, C., Berthier, G., *J. Chim. Phys.* **58**, 169 (1961).
(71) Suthers, B. R., Riggins, P. H., Pearson, D. E., *J. Org. Chem.* **27**, 447 (1962).
(72) Swaney, M. W., Skeeters, M. J., Shreve, R. N., *Ind. Eng. Chem.* **32**, 360 (1940).
(73) Taft, J. C., Jones, M. M., *J. Am. Chem. Soc.* **82**, 4196 (1960).
(74) Taube, H., *Can. J. Chem.* **37**, 129 (1959).
(75) Terentiev, A. P., *Bull. Soc. Chim. France* (4) **35**, 1164 (1924).
(76) Terentiev, A. P., Mogilianskii, Y. D., *Doklady Akad. Nauk S.S.S.R.* **103**, 91 (1955).
(77) Terentiev, A. P., Mogilianskii, Y. D., *J. Gen. Chem. USSR* **28**, 2002 (1958); **31**, 326 (1961) (English trans.).
(78) Thomas, C. A., "Anhydrous Aluminum Chloride in Organic Chemistry," pp. 696ff., Reinhold, New York, 1941.
(79) Thuiller, G., *Bull. Soc. Chim. France* **1959**, 1431.
(80) van Ammers, M., den Hartog, H. J., Haase, B., *Tetrahedron* **18**, 227 (1962).
(81) Vickroy, D. D., Vanderbilt University, unpublished work, 1961.
(82) van Auwers, K., Lange, H., *Ber.* **55**, 1139 (1922).
(83) Walz, D., Fallab, S., *Helv. Chim. Acta* **43**, 549 (1960).
(84) Whitmore, F. C., "Organic Chemistry," pp. 505–6, Van Nostrand, New York, 1937.
(85) Willard, H. H., Dean, J. A., *Anal. Chem.* **22**, 1264 (1950).

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The Reactions of Coordinated Ligands

V. Metal Complexes of β-Mercaptoamines and Their Reactions with Alkyl Halides

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The ligands $NH_2CH_2CH_2SH$, $CH_3N(CH_2CH_2SH)_2$, and $HSCH_2CH_2N{=}C(CH_3)C(CH_3){=}NCH_2CH_2SH$ have been studied. The first forms monomeric complexes, $[Ni(NH_2CH_2CH_2S)_2]$ and $[Co(NH_2CH_2CH_2S)_3]$, and trimeric complex cations, $[M\{M'(NH_2CH_2CH_2S)_2\}_2]^{n+}$ and $[M\{M'(NH_2CH_2CH_2S)_3\}_2]^{n+}$. The second ligand readily forms neutral dimeric complexes of the form $[M_2\{CH_3N(CH_2CH_2S)_2\}_2]$. The tetradentate ligand forms monomeric square planar complexes. Synthetic and kinetic studies reveal that the coordinated mercapto group may be converted into the coordinated thioether function without breaking the metal-sulfur bond. The nucleophilic power of the coordinated mercapto group exceeds that of RSH, but depends on the metal atom. Bridging protects the sulfur atom from alkylation. In the case of nickel(II), alkylation is accompanied by expansion of the coordination number of the nickel from 4 to 6. Ligand reactions have led to the synthesis of planar ligands completely cyclized about the metal ion.

Investigations dedicated to the study of the reactions of coordinated ligands often are most limited by the nonavailability of appropriate well characterized metal complexes, particularly the coordinated mercaptide group. The metal derivatives of simple mercaptans and of chelating dimercaptides like the metal sulfides are usually of very low solubility and, in general, exhibit polymeric structures. A number of years ago, Ewens and Gibson (*8*) demonstrated the reactivity of the coordinated mercaptide function by carrying out the reaction of diethyl-β-mercaptoethylaminegold(III) with alkyl halides (Equation 1). In view of the ability

$$Et_2Au(NH_2CH_2CH_2S) + RX \rightarrow [Et_2Au(NH_2CH_2CH_2S - R)]X \qquad (1)$$

of coordinated metal ions to influence the course of many complex reactions, particularly those which occur in living organisms, a general investigation into the reactivity of the coordinated sulfur atom in the presence of simple alkylating agents might be expected to yield significant results. However, the unavailability of suitable complexes has rendered such studies impossible in the past. In the course of investigations summarized here, a substantial number of monomeric, dimeric, and trimeric complexes of β-mercaptoethylamine and *N*-methyl-bis-β-mercaptoethylamine and similar ligands have been prepared in pure form and characterized. These substances have then been subjected to the action of common alkylating agents and the reactions have been studied in varying detail. The reaction products have been characterized by synthetic means and, in two instances, the results of detailed kinetic measurements have yielded additional information on the nature of this class of reaction.

Complexes of β-Mercaptoamines and Related Ligands

Neutral Complexes of Formulas $M(NH_2CH_2CH_2S)_2$ and $M(NH_2CH_2CH_2S)_3$. Well defined monomeric complexes of nickel(II), palladium(II), and cobalt(III) have been observed to form with β-mercaptoethylamine. The green bis(β-mercaptoethylamine)-nickel(II), NiL_2, was first prepared by Jensen (*15*); however, he was primarily concerned with a general survey of four-coordinate nickel(II) complexes and did not make a detailed characterization of this substance. Jicha and Busch (*16*) determined the magnetic moment of this complex and found it to be diamagnetic, which is consistent with a square planar configuration for nickel(II) (*16*). The same investigators (*16*) prepared yellow bis(β-mercaptoethylamine)-palladium(II), PdL_2. Light blue tris(β-mercaptoethylamine)-cobalt(III), CoL_3, has been prepared by several investigators (*6, 9, 10, 21*) and shown to be diamagnetic (*17*).

These compounds share the common property of being only sparingly soluble in both polar and nonpolar solvents and are readily deposited from strongly basic solutions containing stoichiometric amounts of ligand and metal salt. Although the application of this simple procedure results in the formation of pure crystalline solids in the case of the nickel(II) and palladium(II) complexes, the isolation of the cobalt complex, CoL_3, by the extended air oxidation of the cobalt(II) complex in aqueous solution is difficult because of the gelatinous nature of the solid. Methods based on the displacement of other ligands from the coordination sphere of cobalt(III) by $NH_2CH_2CH_2S^-$ have been more successful (Equations 2 and 3).

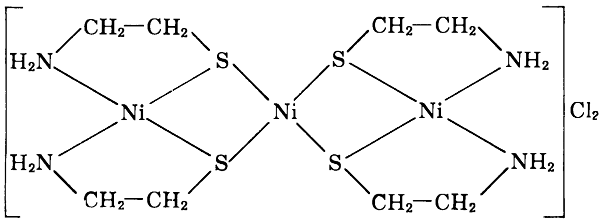
$$Co(EDTA)^- + 3NH_2CH_2CH_2S^- \rightarrow Co(NH_2CH_2CH_2S)_3 + EDTA^{-4} \qquad (2)$$

$$Co(NH_3)_6{}^{+3} + 3NH_2CH_2CH_2S^- \rightarrow Co(NH_2CH_2CH_2S)_3 + 6NH_3 \qquad (3)$$

The unsymmetrical nature of β-mercaptoethylamine should lead to geometric isomerism among its metal complexes. cis and trans isomers might be expected with the square planar nickel(II) and palladium(II) derivatives and facial and peripheral isomers with cobalt(III). However, during the course of the preparation of various samples in which the procedure and experimental conditions were varied, no evidence of such isomerism was apparent (*6, 15*). This is particularly evident in the case of the cobalt(III) complex, CoL_3. Samples prepared by the addition of cobalt(II) chloride 6-hydrate to strongly basic aqueous solution of the ligand and by displacement of ammonia and (ethylenedinitrilo)-

tetraacetate from the corresponding complexes were found to have indistinguishable infrared spectra and identical physical properties (*6*). The methods usually employed in the separation of geometrical isomers are experimentally impractical in view of the very slight solubilities of the uncharged species. It has been suggested (*6*, *15*) that the known isomers of ML_2 and CoL_3 are associated with mutual cis coordination of all the mercaptide functions in the coordination sphere. This is consistent with the pi-bonding tendencies of the donor atoms and the symmetry of the appropriate central atom *d* orbitals (*6*). This conclusion provides a ready explanation for the structures and properties of the trinuclear derivatives of ML_2 and ML_3.

Trinuclear Cations Derived from $M(NH_2CH_2CH_2S)_2$ and $Co(NH_2CH_2CH_2S)_3$. In his early observations on the complexes of β-mercaptoethylamine, Jensen (*15*) reported the formation of a second nickel(II) derivative of that ligand. This was isolated as green, water-soluble crystals. Jensen suggested that the ligand might be coordinated in the form of the zwitter ion, $NH_3CH_2CH_2S$; however, he offered no evidence in support of this contention. Jicha and Busch (*16*) prepared this material by two methods and measured a number of its physical properties. This dark green solid has been isolated in the form of three different salts, all of which display the unusual stoichiometry, $Ni_3(NH_2CH_2CH_2S)_4X_2$, where X is Cl, Br, or I. The molar magnetic susceptibility (Table I) reveals that the three nickel(II) atoms are all diamagnetic and, therefore, presumably coordinated in a square planar fashion. Solutions of the salts in water behave as uni-divalent electrolytes, as indicated by molar conductance (Table II). Evidence has also been obtained, by the method of continuous variations, for the existence of materials of the same composition in dilute solutions (*16*). These considerations led to the assignment of structure I to this novel complex ion. Structure II is a simplified representation of the same substance. Structure I requires the cis orientation of the two sulfur atoms in NiL_2. On the basis of structure I, procedures have been devised for the synthesis of $Ni(NiL_2)_2^{+2}$ from the neutral bis complex, NiL_2 (Equation 4).



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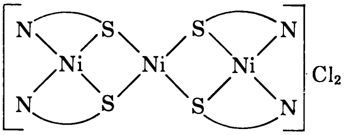


II

$$2Ni(NH_2CH_2CH_2S)_2 + Ni^{+2} \rightarrow [Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]^{+2} \qquad (4)$$

The preparation of the trinuclear nickel(II) complex by solubilization of the uncharged bis species with nickel(II) ion has been generalized by the use of

Table I. Molar Susceptibilities[a] and Magnetic Moments of Complexes of β-Mercaptoethylamine

Compound	$\chi \times 10^{-6}$ *(Complex)*	*T,° K.*	$\mu_{eff.}$ *(B.M.) per Metal Ion*
$[Ni(NH_2CH_2CH_2S)_2]$	−98.7	300	..
$[Co(NH_2CH_2CH_2S)_3]$	−55.4	300	..
$[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl_2$	−339.0	300	..
$[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]Br_2$	−282.2	305	..
$[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]I_2$	−205.4	305	..
$[Pd\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl_2$	−86.9	302	..
$[Cu(II)\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl_2$	+452.1	305	1.03
$[Cu(I)\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl$	−75.9	305	..
$[Cd\{Ni(NH_2CH_2CH_2S)_2\}_2][CdCl_4]$	−291.9	303	..
$[Hg\{Ni(NH_2CH_2CH_2S)_2\}_2][HgCl_4]$	+6732.0	305	2.95
$[Hg\{Ni(NH_2CH_2CH_2S)_2\}_2][HgBr_4]$	+5938.4	305	2.79
$[Hg\{Ni(NH_2CH_2CH_2S)_2\}_2][HgI_4]$	−474.1	302	..
$[Cd\{Ni(NH_2CH_2CH_2S)_2\}_2][HgI_4]$	−216.3	305	..
$[Ni\{Pd(NH_2CH_2CH_2S)_2\}_2]Cl_2 \cdot 2H_2O$	−142.1	302	..
$[Co\{Co(NH_2CH_2CH_2S)_2\}_2]Cl_2$	+7324.9	304	2.49
$[Co\{Co(NH_2CH_2CH_2S)_3\}_2Br_3$	−118.8	303	..
$[Ni\{Co(NH_2CH_2CH_2S)_3\}_2]Br_2$	+3983.6	303	3.23

[a] Molar susceptibilities of ligand and anions (using Pascal's constants). $NH_2CH_2CH_2S^-$, -50.13×10^{-6}; Cl^-, -20.1×10^{-6}; Br^-, -30.6×10^{-6}; I^-, -44.6×10^{-6}

Table II. Molar Conductances of Complexes of β-Mercaptoethylamine

T = 25° C.

Compound	λ_m, *Ohm*$^{-1}$
$[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl_2$	242
$[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]Br_2$	245
$[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]I_2$	246
$[Pd\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl_2$	244
$[Cu(II)\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl_2$	184
$[Pt\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl_2$	238
$[Pd\{Pd(NH_2CH_2CH_2S)_2\}_2]Cl_2$	238
$[Ni\{Pd(NH_2CH_2CH_2S)_2\}_2]Cl_2 \cdot 2H_2O$	258
$[Cu(I)\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl$	127
$[Cd\{Ni(NH_2CH_2CH_2S)_2\}_2][CdCl_4]$	442
$[Cd\{Cd(NH_2CH_2CH_2S)_2\}_2][CdCl_4]$	423
$[Co\{Co(NH_2CH_2CH_2S)_2\}_2]Cl_2$[a]	148
$[Co\{Co(NH_2CH_2CH_2S)_3\}_2]Br_3$	362
$[Ni\{Co(NH_2CH_2CH_2S)_3\}_2]Br_2$	231

[a] Molar conductance determined in methanol.

solutions of other divalent and monovalent metal ions as solubilizing media. A substantial array of trinuclear complexes containing two different metal ions has been isolated in the course of such studies by Jicha and Busch (*17*). Complex ions containing more than one kind of metal ion are relatively rare, despite the strong bridge-forming tendency associated with the mercaptide group. NiL_2 has been combined by bridge formation with Pd(II), Cu(II), Cu(I), Hg(II), Cd(II), and Pt(II). The molar susceptibilities and magnetic moments and the molar conductances of the resultant polymetallic complexes are summarized in Tables I and II. Typical equations for the formation of such species are given below. Continuous variation studies have been particularly revealing in these systems, since they show, for example, that 1 mole of Pd(II) combines with 2 moles of NiL_2 in dilute solution. This result obviates the possibility that the trinuclear species is limited in existence to the solid state. The magnetic moments and molar conductances of the pure substances of the composition $[M(NiL_2)_2]^{+2}$ are consistent with the structures proposed, with the single exception of the mercury(II) derivatives in which it must be presumed that the Hg(II) ion impairs the donor ability of the mercaptide function to the extent that it no longer causes spin pairing in the mixed metal derivative with Ni(II).

$$2[Ni(NH_2CH_2CH_2S)_2] + M^{+2} \rightarrow [M\{Ni(NH_2CH_2CH_2S)_2]^{+2} \qquad (5)$$

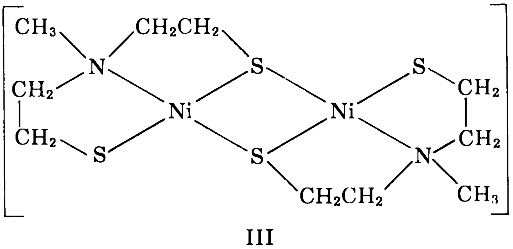
$$2[Ni(NH_2CH_2CH_2S)_2] + M'Cl_4^{-2} \rightarrow [M'\{Ni(NH_2CH_2CH_2S)_2\}_2]^{+2} + 4Cl^- \qquad (6)$$

$$(M = Cd^{+2} \text{ or } Cu^{+2};\ M' = Pd^{+2} \text{ or } Pt^{+2})$$

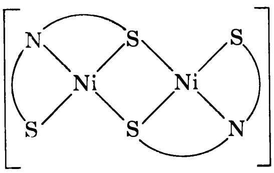
As the data summarized in Tables I and II show, both Pd(II) and Co(II) form homometallic trinuclear complexes of the general structure$[M(ML_2)_2]X_2$. Also, the mononuclear Pd(II) complex has been utilized to form heterometallic trinuclear species—e.g., $[Ni(PdL_2)_2]X_2$.

The bridge-forming proclivity of the neutral cobalt(III) complex, CoL_3, has also been demonstrated (*6*). Two trinuclear compounds of the formula $[M(CoL_3)]X_n$, where M is Ni(II) or Co(III), have been isolated in pure form. Detailed study of these substances indicates that the complex CoL_3 forms three mercaptide bridges to the third metal ion, thus providing octahedral coordination of the six sulfur atoms about that ion. Data on these unusual compounds are also included in Tables I and II.

Complexes of Methyl-2,2′-dimercaptodiethylamine. Nickel(II), palladium(II), and cobalt(II) form stable complexes in ammoniacal solution with methyl-2,2′-dimercaptodiethylamine. These compounds exhibit a stoichiometry of one metal ion per ligand anion. Bis (methyl-2,2′-dimercaptodiethylamine)dinickel(II), Ni_2L_2, was first prepared by Harley-Mason (*12*), who proposed a dimeric structure (structures III and IV) for this nonelectrolyte on the basis of its molecular weight as determined cryoscopically in ethylene dibromide. Samples of this compound, prepared by Harley-Mason's procedure and recrystallized from methanol, were found by Jicha and Busch (*18*) to be essentially diamagnetic, in agreement with the proposed structure. Further, the later investigators point out that the usual pyramidal structure of three covalent sulfur (II) suggests that the coordination spheres of the two metal ions will not be coplanar. This leads to a V-shaped configuration for the molecule and the substance should exist as a mixture of optical antipodes. The compound Ni_2L_2 is only slightly soluble in water and soluble in halogenated solvents such as chloroform, bromoform, trichloroethylene, and ethylene dibromide. Yellow-orange blis(methyl-2,2′-dimercaptodiethylamine) dipalladium(II), Pd_2L_2, can be prepared from aqueous ammonia solution using stoichiometric quantities of potassium tetrachloropalladate(II) and ligand. This substance bears a very close resemblance to the corresponding nickel(II) complex in its physical properties and structure.

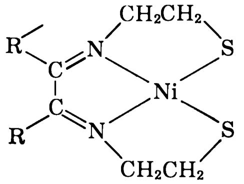


III



IV

Complexes of 2,2′-Dialkyl(ethanediylidenedinitrilo)diethanethiols. The previously unknown Schiff base derivatives of α-diketones with β-mercaptoalkylamines should be ideally suited to form metal complexes in which the ligand is coordinated in a planar tetradentate manner. Further, the mercaptide functions should occupy cis positions in the coordination sphere of the metal ion. Structure V illustrates the structure expected for such substances. Three products might



V

be expected from the reaction of an α-diketone with a mercaptoamine: the Schiff base, the thiazoline, and the mercaptal. Mercaptals have been found to be of no significance under the conditions of the reactions studied in these laboratories (*23*). Thiazolines, however, form readily in all cases and appear to be the dominant products, as found, for example, in the reaction of biacetyl with *o*-aminobenzenethiol. In similar reactions with β-mercaptoethylamine, thiazolines are normally formed in greater than 50% yield. Thompson and Busch (*23*) have shown that the addition of nickel(II) acetate shortly after initiation of the condensation greatly improves yields of the desired Schiff base. Under these conditions, the Schiff base was isolated in the form of its complex with nickel(II) ion. This reaction provides a dramatic example of the role played by a metal ion in facilitating the formation of an organic molecule that is otherwise strongly discriminated against by competing reactions. In effect, the metal ion brings the reactants together in the product form that is most favorable for complexation.

The procedure of Thompson and Busch (*23*) has resulted in the synthesis of 2,2′-dimethyl(ethanediylidenedinitrilo)diethanethiolonickel(II), Ni(BE); 2-methyl-2′-ethyl(ethanediylidenedinitrilo)diethanethiolonickel(II), Ni(PE); and 2-methyl-2′-pentyl(ethanediylidenedinitrilo)diethanethiolonickel(II), Ni(OE) in yields of 70 to 78%. The magnetic moments of these complexes all confirm the expected planar coordination of the Ni(II) ion. Molecular weight determinations have shown the substances to be monomeric in dichloroethylene, while infrared data and total elemental analyses further support the assigned structures. The complexes are highly colored, appearing green to reflected light and red-brown to transmitted light. They exhibit considerable solubilities in water, acetone, nitrobenzene, and bromobenzene. The colors of the solutions of these compounds vary strongly from solvent to solvent, generally ranging from violet-purple in benzene to red-brown in water. The color in pyridine more nearly resembles that in benzene and in chloroform than that in water. In view of the fact that pyridine is the strongest coordinating agent among these solvents, while chloroform and benzene are among the weaker, it was concluded that this effect on the charge transfer spectrum is not associated with the expansion of the coordination number of the nickel(II) ion.

Reaction of Coordinated Mercaptide Group with Alkyl Halides

Early observations regarding reactions of this class were made by Ewens and Gibson (*8*), who studied the reaction of (β-mercaptoethylamine)diethylgold(III) with methyl iodide and ethyl bromide. This novel and interesting example of an addition reaction occurring without destruction of the complex was complicated by the formation of oils, and pure compounds could be isolated as solids only in the form of picrate salts.

The synthesis of a large number of metal complexes of mercaptoamines by Busch and coworkers (*6*, *15*, *17*, *24*) has opened the way for detailed study of the reactions of the coordinated mercaptide function. Mercaptoamine complexes provide the first extensive series of complexes of known structure in which the effect of varying structural parameters on the reactivity of the mercaptide group can be subjected to investigation.

Synthesis of S-Alkyl-β-mercaptoethylamine Complexes by Alkylation of β-Mercaptoethylamine Compounds. Jicha and Busch (*18*) have reported studies on the reactions of the nickel(II) and palladium(II) complexes of β-mercaptoethylamine with methyl iodide and benzyl halides. Superficially, the most typical of these experiments were concerned with the reactions of bis(β-mercaptoethylamine)-nickel(II) with alkyl halides in dimethylformamide as the solvent. Despite the unfavorable solubility of the nickel(II) complex in dimethylformamide, the alkylation reactions have been observed to proceed at room temperature, resulting in dissolution of the complex. In the case of methyl iodide, the reaction proceeds to completion in approximately 2 hours, during which time the color of the solution undergoes a gradual change from a deep red to an emerald green. The ready solubility of the product in dimethylformamide facilitates the separation of the final product from the unreacted starting material. Removal of the dimethylformamide in vacuo produces a green oil which can be induced to crystallize upon the addition of cold absolute ethanol, yielding a light green solid.

Analysis of the solid from the reaction of the nickel(II) complex NiL_2 with methyl iodide reveals a stoichiometry of 1 nickel(II):$2NH_2CH_2CH_2S-CH_3$:2 iodides. The infrared spectrum displays two sharp bands of medium intensity at 3263 and 3216 cm.$^{-1}$, which are characteristic of the $-NH_2$ asymmetric and symmetric stretching frequencies. A third band of comparable intensity occurs at 1578 cm.$^{-1}$ with a shoulder at 1588 cm.$^{-1}$, which can be attributed to the $-NH_2$ deformation mode. The appearance of these bands confirms the presence of a primary amine. On the basis of these spectral observations, the electrophilic nature of the attacking alkyl group, and the usual inability of the coordinated amine-nitrogen to undergo chemical reactions (*4*, *5*), methylation of the ligand is presumed to occur at the coordinated sulfur atom (Equation 7). The alkylation

$$[Ni(NH_2CH_2CH_2S)_2] + 2CH_3I \xrightarrow{DMF} [Ni(NH_2CH_2CH_2SCH_3)_2I_2] \qquad (7)$$

of $[Ni(NH_2CH_2CH_2S)_2]$ was also carried out using benzyl halides under the same conditions, and the dibenzylated products were isolated.

$$[Ni(NH_2CH_2CH_2S)_2] + 2C_6H_5CH_2X \searrow [Ni(NH_2CH_2CH_2S{-}CH_2C_6H_5)_2X_2] \qquad (8)$$

where X = Cl–, Br–, or I–.

In these cases, the rate of alkylation might be expected to be dependent upon the particular benzyl halide used. Indeed, a significant variation was observed, with the rate of benzylation increasing in the order: $C_6H_5CH_2Cl < C_6H_5CH_2Br < C_6H_5CH_2I$.

The reaction of tetrakis(β-mercaptoethylamine)trinickel(II) iodide, $[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]I_2$, with methyl iodide was found to result in the formationtion of a product which is identical to that obtained by methylation of $[Ni(NH_2CH_2CH_2S)_2]$ (Equation 9).

$$[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]I_2 + 4CH_3I \overset{DMF}{\searrow} 2[Ni(NH_2CH_2CH_2S{-}CH_3)_2I_2] + NiI_2 \qquad (9)$$

In this case the greater solubility of the trimeric complex in dimethylformamide produces a smoother reaction without apparent contamination. Similarly, $[Ni(NH_2CH_2CH_2S{-}CH_2C_6H_5)_2Cl_2]$ and $[Ni(NH_2CH_2CH_2S{-}CH_2C_6H_5)_2Br_2]$ can be prepared by reacting the chloride and bromide salts of the trimeric complex with benzyl chloride and benzyl bromide, respectively. However, chloride and bromide salts of the trimeric species are considerably less soluble in DMF than is the corresponding iodide.

The observations reported above on the alkylation of the trimeric complex species, $[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]^{+2}$, have an important bearing on the reaction of the neutral complex, $[Ni(NH_2CH_2CH_2S)_2]$. When $[Ni(NH_2CH_2CH_2S)_2]$ is treated with alkyl halides, the trimeric complex forms in solution and can be isolated if the reaction is interrupted. The appearance of this species as a stable intermediate indicates that the alkylation reaction of $[Ni(NH_2CH_2CH_2S)_2]$ proceeds in a stepwise fashion (Equations 10 to 13).

$$[Ni(NH_2CH_2CH_2S)_2] + 2RX \rightarrow [Ni(NH_2CH_2CH_2S{-}R)_2X_2] \qquad (10)$$

$$[Ni(NH_2CH_2CH_2S{-}R)_2X_2] + 2[Ni(NH_2CH_2CH_2S)_2] \searrow [Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]X_2 + 2NH_2CH_2CH_2S{-}R \qquad (11)$$

$$[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]X_2 + 4RX \searrow 2[Ni(NH_2CH_2CH_2S{-}R)_2X_2] + Ni^{+2} + 2X^- \qquad (12)$$

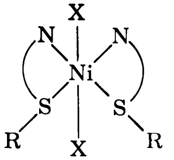
$$Ni^{+2} + 2X^- + 2NH_2CH_2CH_2SR \rightarrow [Ni(NH_2CH_2CH_2S{-}R)_2X_2] \qquad (13)$$

The first step might be considered to involve alkylation of the small amount of the uncharged bis complex which is in solution. According to Equation 11, $[Ni(NH_2CH_2CH_2S)_2]$ is a more strongly coordinated ligand than $NH_2CH_2CH_2S{-}R$, a relationship leading to the displacement reactions shown—i.e., formation of $[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]^{+2}$. The excess alkylating agent then attacks the soluble trimeric species, leading to the formation of the observed product as shown in Equations 12 and 13.

An alternative process involving the direct alkylation of $[Ni(NH_2CH_2CH_2S)_2]$ might also be suggested (in place of Equation 12). This possibility may be associated with an equilibrium between the trimeric species and the uncharged bis complex in solution. On the basis of the evidence presented at this point, the particular species which undergoes alkylation is still somewhat in doubt. The isolation of the alkylated complexes in yields greater than 66.67% is indicative of complex formation between the solvated nickel(II) ions and the free alkylated ligand formed during the reaction (as indicated by Equation 13).

The solid products obtained using methyl iodide and benzyl iodide exhibit magnetic moments of 3.18 and 3.09 Bohr magnetons, respectively (*18*). These magnetic moments correspond to values typical of two unpaired electrons in structures involving octahedral nickel(II). Consequently, these compounds are formulated as $[Ni(NH_2CH_2CH_2S{-}CH_3)_2I_2]$ and $[Ni(NH_2CH_2CH_2S{-}CH_2C_6H_5)_2$-

I_2]. The substantial solubilities of these compounds in chloroform and other less polar organic solvents are in agreement with their formulation as nonelectrolytes. In methanol at 25° C., the molar conductivities of 166 and 167 ohm^{-1} for [Ni($NH_2CH_2CH_2S-CH_3$)$_2I_2$] and [Ni($NH_2CH_2CH_2S-CH_2C_6H_5$)$_2I_2$], respectively, are characteristic of di-univalent electrolytes in this solvent, indicating almost complete solvolysis of the coordinated iodide ions in this relatively polar solvent. Decomposition of these complexes was observed upon dissolving in water. Visible and near-infrared spectra results are also consistent with structure VI.



VI

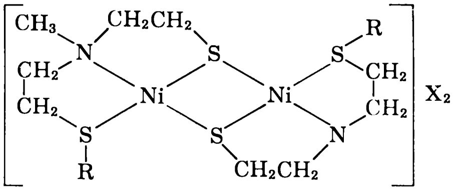
Alkylation of the uncharged bispalladium(II) complex, [Pd($NH_2CH_2CH_2S$)$_2$], proceeds somewhat differently under the conditions employed for the corresponding nickel(II) complex. Allowing the reaction mixture to stir for several hours at slightly above room temperature results in the formation of a red solution, which upon concentration and the addition of cold ethanol yields a red solid having a stoichiometry of 1 Pd(II):1 $NH_2CH_2CH_2S-CH_3$:2I$^-$. This compound is only slightly soluble in ethanol and chloroform. It can be recrystallized from warm ethanol with no apparent decomposition. The formulation of this compound as the nonelectrolyte, [Pd($NH_2CH_2CH_2S-CH_3$)I_2], is in agreement with these solubility properties and the coordination number of 4 for palladium(II). The ease of formation of the monoalkylated complex is also dependent upon the particular alkyl halide employed. The reaction of benzyl bromide with [Pd($NH_2CH_2CH_2S$)$_2$] resulted in the isolation of a solid having a composition suggestive of a mixture of [Pd($NH_2CH_2CH_2S-CH_2C_6H_5$)$_2$]Br_2 and [Pd($NH_2CH_2CH_2S-CH_2C_6H_5$)Br_2]. This behavior is in accord with the lesser coordinating ability [toward palladium(II)] of bromide ion as compared to iodide ion.

Experiments have shown that these complexes will react with dihalogen compounds to form new chelate rings, converting two bidentate ligands into a single tetradentate ligand *in situ*. Identical products are obtained from the ligand reaction between NiL_2 and α,α′-dibromo-*o*-xylene, and by first preparing the tetradentate ligand and then forming the complex from that ligand and nickel(II) bromide. Both products were isolated as light blue powders of the composition Ni($NH_2CH_2CH_2S$)$_2$.C_6H_4(CH_2Br)$_2$. The magnetic moments of the materials are very close to the value of 3 Bohr magnetons, which is expected for structures containing octahedral nickel(II). The latter result implies coordination of the bromide ions to the nickel atom, in addition to tetradentate coordination by the organic ligand.

The use of dimethylformamide as the solvent medium in these reactions merits further discussion. In view of the ease of dissolution of many inorganic salts in this solvent at room temperature, the apparent success encountered in the alkylation of the coordinated sulfur atom in [Ni($NH_2CH_2CH_2S$)$_2$] may arise from the solubility of the intermediate [Ni{Ni($NH_2CH_2CH_2S$)$_2$}$_2$]X_2 formed during the reaction. Moreover, Kornblum and Blackwood (*19*) have reported that under conditions similar to those employed for the above reactions, dimethylformamide also undergoes alkylation; however, such reactions are reported to be slow, and in the case of 0.2*M* solutions of methyl iodide and benzyl bromide in dimethylformamide at 25° to 30° C., the reaction is only 10% complete after 12 and 19 days, respectively. Interference by this solvent reaction is obviated in view of the more rapid alkylation of the coordinated sulfur atom.

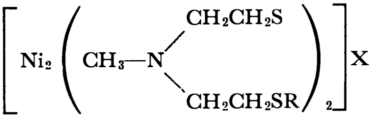
Synthesis of *S*-Alkyl-*N*-methyl-2,2′-dimercaptodiethylamine by Direct Alkylation of Complexes M_2L_2. The nickel(II) and palladium(II) complexes of methyl-2-,2′-dimercaptodiethylamine, $[M_2\{CH_3N(CH_2CH_2S)_2\}_2]$, exhibit a similar tendency to undergo reaction with methyl iodide and benzyl bromide (*18*). The extreme solubilities of these complexes in chloroform allow the alkylation reaction to be conducted homogeneously. In the case of $[Ni_2\{CH_3N\text{-}(CH_2CH_2S)_2\}_2]$, only one chloroform-soluble product has been isolated, regardless of the quantity of methyl iodide or benzyl bromide used. The red-brown methylated derivative and the brown benzylated derivative can be isolated with a certain degree of difficulty after concentration of the respective chloroform solutions and trituration with cold absolute ethanol and benzene.

Analytical data on the soluble products isolated from chloroform are in excellent agreement with the composition: 1 Ni^{+2}:1 monoalkylated ligand:1 I^- or Br^-. The magnetic moment of this methylated complex was found to be 1.89 Bohr magnetons per nickel(II). The molar conductivities of the methylated and benzylated complexes in methanol at 25° C. are 75.4 and 68.4 ohm^{-1}, respectively. These values approximate those expected for uni-univalent electrolytes in this solvent. The formulation of these alkylated compounds as dimeric electrolytes (structure VII) does not appear to be totally consistent with their physical properties. One or both halide ions may be bound to the metal ion. These results lead to the easily understood generalization that terminal sulfur atoms alkylate more readily than bridged mercaptide groups.



VII

Kinetics and Mechanism of Reactions of Bis(methyl-2,2′-dimercaptodiethylamine)dinickel(II) with Alkyl Halides. The rates of reaction of $[Ni_2\{CH_3N\text{-}(CH_2CH_2S)_2\}_2]$, structure III, with methyl iodide, benzyl bromide, benzyl chloride, *p*-chlorobenzyl chloride, and *p*-nitrobenzyl chloride have been studied as functions of temperature and concentration in chloroform (3). Absorbance measurements were utilized to determine the rates. All experiments were conducted with excess alkyl halide (20 to 1000 times the initial concentration of complex). Jicha and Busch (*18*) were able to isolate alkylated complexes of the composition

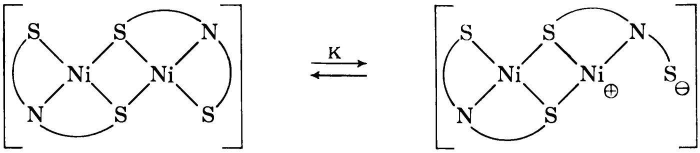


$$\left[Ni_2\left(CH_3{-}N\begin{matrix}CH_2CH_2S\\ CH_2CH_2SR\end{matrix}\right)_2\right]X_2$$

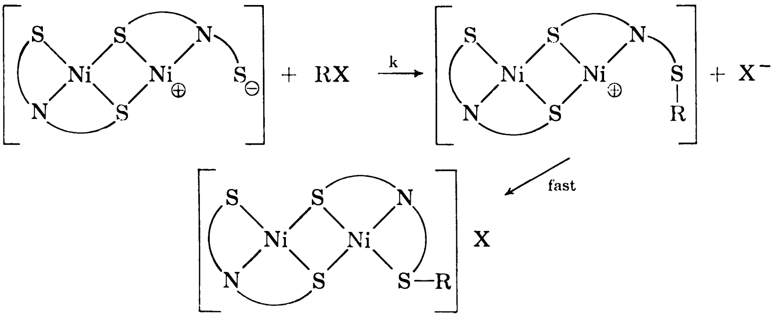
and these substances were consequently expected to be the products of the reactions under kinetic investigation.

Since these reaction products exhibit considerable absorbance at the wave lengths utilized in the rate measurements, the calculation of rate constants required a technique incorporating this factor. Two methods of calculation were employed successfully. In some cases, limiting absorbances (A_{00}) were determined and the rates were obtained from the slopes of graphs of log $(A_0—A_{00})/(A—A_{00})$ *vs.* time. These served to demonstrate the pseudo-first-order nature of the rate constant; however, the more general calculation procedure was that due to Guggenheim (*11*). The first-order dependence of the rate on the concentration of alkyl halide was shown by varying initial concentrations.

The simple second-order nature of the kinetics in this system leads to immediate conclusions of some consequence. The rate-determining step is clearly not the heterolytic breaking of a metal-sulfur bond to produce the free $R\text{-}S^-$ group, which then might undergo reaction. Further, the fact that there is no evidence suggesting consecutive processes eliminated the possibility that any such scheme could enter into the total rate except essentially as a pre-equilibrium—e.g., Equations 14 and 15.



(14)

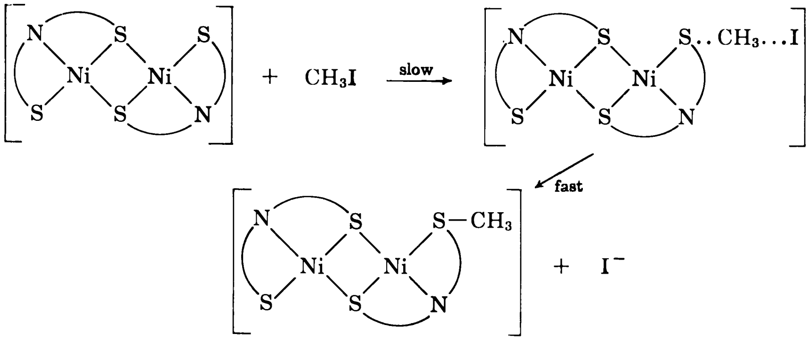


(15)

In view of the fact that the complex in question is of the diamagnetic inert class, a significant pre-equilibrium of this kind is not concluded to be highly likely.

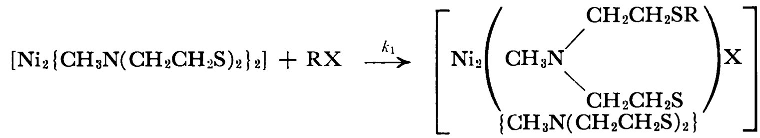
Consideration has been given to the ligand field implications of a process involving an S_N1 mechanism in the square planar d^8 case. Although this particular example has not previously been calculated, it is readily estimated from the data given by Basolo and Pearson (*1*). The loss in stabilization energy is estimated to be 13.62 Dq. This suggests a contribution to the activation energy in excess of that expected for the corresponding S_N1 process involving even the most inert octahedral configurations (d^6 as in Co^{+3}). The cobalt(III) octahedral case is associated with a loss in stabilization energy of only 4 Dq. and its substitution reactions commonly reveal activation energies of some 20 to 30 kcal. per mole (*2*). It is usually suggested that substitution reactions involving inert planar ions occur by the formation of additional bonds above and below the plane of the four original donor atoms. Chloroform is assumed to be too weak a donor molecule to serve this function. Processes of this general type are more probable in solvents of greater coordinating ability.

It is much more in keeping with the properties of this reactant to presume a less contrived interpretation of the rate data. The coordinated sulfur atom may be assumed to act as a nucleophile, directly displacing the halide ion from the alkyl halide, as illustrated in Equation 16.

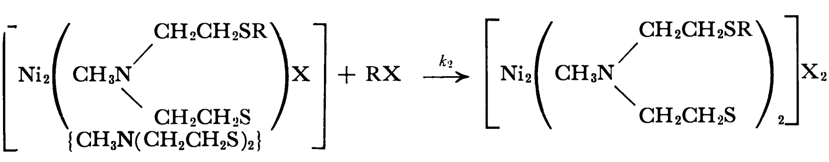


(16)

The absence of consecutive rate processes also justifies the conclusion that the reaction of the first mole of alkyl halide with the complex is relatively slower than the reaction of the second ($k_1 < < k_2$).



$$[Ni_2\{CH_3N(CH_2CH_2S)_2\}_2] + RX \xrightarrow{k_1} \left[Ni_2\left(CH_3N\begin{matrix} CH_2CH_2SR \\ CH_2CH_2S \end{matrix}\right)\{CH_3N(CH_2CH_2S)_2\}\right]X \qquad (17)$$



$$\left[Ni_2\left(CH_3N\begin{matrix} CH_2CH_2SR \\ CH_2CH_2S \end{matrix}\right)\{CH_3N(CH_2CH_2S)_2\}\right]X + RX \xrightarrow{k_2} \left[Ni_2\left(CH_3N\begin{matrix} CH_2CH_2SR \\ CH_2CH_2S \end{matrix}\right)_2\right]X_2 \qquad (18)$$

This is in agreement with the suggestion that the reactions are essentially S_N2 in character, with the coordinated sulfur atom serving as the nucleophile. The conversion of the mercaptide group into a thioether group results in a weakened total ligand field, since the latter is a weaker complexing agent. This, in turn, should lead to the increased nucleophilic power of the single terminal mercaptide group in the monoalkylated intermediate.

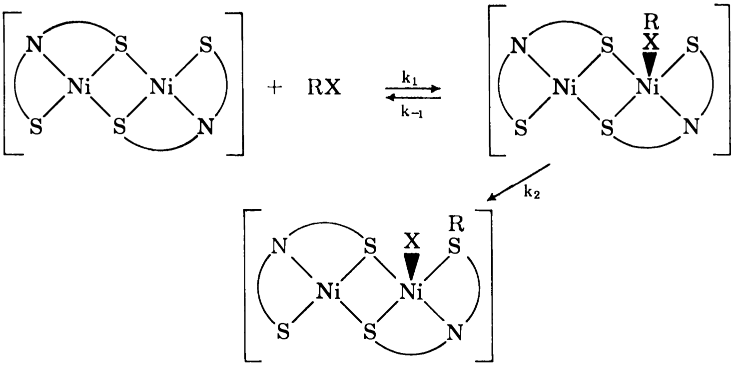
The relative rates and the parameters characterizing the temperature dependences of the rates are summarized in Table III. The outstanding features of the activation energies are their regularity and small values. The only strikingly different value is that found in the case of benzyl bromide and this is somewhat lower than the others. In view of the prediction by crystal field theory that dissociation of a planar complex should involve large activation energies, the values given in Table III may be considered as negative evidence in support of the S_N2 mechanism proposed above.

It is, in fact, true that the temperature dependence studies provide the only substantial evidence suggestive of an additional mode of interaction between the alkyl halide and the complex. The magnitudes of the observed activation energies are much smaller than those usually associated with nucleophilic substitution at the saturated carbon atom (15 to 30 kcal. per mole) (*13*, *22*). This might arise from some sort of pre-equilibrium.

Table III. Relative Rates, Energies of Activation, and Frequency Factors for Reactions of $[Ni_2\{CH_3N(CH_2CH_2S)_2\}_2]$ with RX at 25° C. in Chloroform

RX	k_{av}, *L./Mole/Min.*	*k* *Relative*	E_a, *Kcal./Mole*	*A*, *L./Mole/Min.*
CH_3I	0.251	21.1	10.7	1.4×10^7
$C_6H_5CH_2Br$	1.49	125	6.91	1.8×10^5
$C_6H_5CH_2Cl$	1.19×10^{-2}	1.00	12.6	1.9×10^8
p-$ClC_6H_4CH_2Cl$	8.30×10^{-3}	0.70	11.6	2.4×10^6
p-$NO_2C_6H_4CH_2Cl$	6.38×10^{-3}	0.54	12.2	5.0×10^6

The tendency of planar ions to associate to some extent with additional groups above the planar array of ligands provides a possible source of a kinetically significant pre-equilibrium. The reacting alkyl halide might serve this function, coordinating weakly to the metal ion previous to the rate-determining step. The advent of such an equilibrium would produce a reaction scheme of the type given in Equation 19.



(19)

Jicha (*17*) has shown that the halide ion produced in reactions of this sort is usually coordinated to the metal ion in the final product. For the process given above,

$$\text{Rate} = \left(\frac{k_1k_2}{k_{-1}}\right)(\text{complex})(\text{RX}) \tag{20}$$

A number of investigators (*13*) have suggested that the prior coordination of a metal ion to the halogen atom of an alkyl halide increases the S_N1 character of the transition state for nucleophilic substitution at the saturated carbon atom. Such effects should be liable to detection through the use of properly altered structural parameters (*14*). The establishment of such an effect should justify a pre-equilibrium of the sort considered in the preceding paragraph. This should provide a much more sensitive test for such processes, since success of the obvious alternative equilibrium methods depends on a favorable ratio of the equilibrium concentrations of the several species involved. From among the data obtained in the studies reported here, the relative rates of reaction of benzyl chloride and the *p*-nitro analog are most significant in this respect. Kornblum *et al.* (*20*) have shown that the reaction of *p*-nitrobenzyl bromide with silver nitrite proceeds at less than one tenth the rate found for benzyl bromide itself. On the other hand, these two substances react with pyridine by an S_N2 mechanism at almost equivalent rates. As the data in Table III indicate, the rate of reaction of the complex $[Ni_2\{CH_3N(CH_2CH_2S)_2\}_2]$ with *p*-nitrobenzyl chloride is approximately one half the value for the reactions with benzyl chloride. The difference in rates is too small to support a strong electrophilic catalysis of the nucleophilic substitution reaction. However, the interaction of nickel(II) with halogen is relatively weak (as compared to Ag^+ and Hg^{+2}) even under ideal conditions. In consequence, the data presented to this point cannot be considered to have adequately tested the occurrence of this part of the mechanism suggested above.

Kinetics and Mechanism of Reactions of Tetrakis (β-mercaptoethylamine)-trinickel(II) Chloride, $Ni_3(NH_2CH_2CH_2S)_4Cl_2$, with Alkyl Halides. Jicha has shown that tekrakis(β-mercaptoethylamine)trinickel(II) chloride and bis (β-mercaptoethylamine)nickel(II) react with alkyl halides to yield the same product. Tetrakis (β-mercaptoethylamine)trinickel(II) chloride was chosen as a reactant in kinetic experiments because of its solubility and intense red color in contrast to the insoluble, green bis(β-mercaptoethylamine)nickel(II) which would have been the better of the two for chemical simplicity.

Solubility relationships revealed that methanol is the best solvent for the study of the reactions of $[Ni(NiL_2)_2]Cl_2$ with alkyl halides. All the reactants of interest either react with methanol or undergo deleterious side reactions. Consequently, the relative rates of these processes had to be estimated in order to establish the feasibility of the study of interest and make any necessary corrections.

The competing processes were sufficiently slower than the reaction of interest only in the case of the nickel complex, $[Ni(NiL_2)_2]Cl_2$. Attempts to determine the rate of reaction of $[Pd(NiL_2)_2]Cl_2$ with benzyl bromide revealed a very slow process occurring at a rate comparable to, but slightly slower than, the solvolysis of benzyl bromide. It is concluded that the rate of reaction of this complex with benzyl bromide is too slow for accurate rate study in methanol.

All data obtained on the rate of reaction of $[Ni(NiL_2)_2]Cl_2$ with alkyl halides—i.e., methyl iodide, benzyl bromide, benzyl chloride, *p*-nitrobenzyl chloride, *p*-chlorobenzyl chloride, ethyl bromide, ethyl iodide, *n*-propyl bromide, and *n*-propyl iodide—conform closely to a pseudo-first-order rate law. Almost all experiments were carried out in the presence of an excess of alkyl halide. Since methanol solutions of the alkylated complexes have only negligible absorption at 495 mμ, rates were obtained by graphs of log $A_0 - A$ *vs.* time. The graphs are linear over the entire time interval, which corresponds to more than two half lives in most cases, passing through the origin at zero time. The rate is essentially the same whether measured by the spectrophotometric or conductivity method.

The reaction is also first order with respect to the concentration of alkyl halide. Relative rates and activation energies are summarized in Table IV. The relative rates are not very different from those found in the case of bis(methyl-2,2′-dimercaptodiethylamine)dinickel(II). The rates found with the straight-chain, aliphatic halides are affected in the normal manner. The rate decreases as chain length increases, with the greatest decrease arising from the addition of the second carbon atom. Each subsequent carbon atom has a smaller effect on the rate. The order of reactivity with respect to the halide used is also normal ($Cl < Br < I$) for both the benzyl and aliphatic halides. Although a strong autocatalytic effect is observed with isopropyl bromide, some information can be gained from the initial rates. It appears that the rate constant is the same as that obtained for *n*-propyl bromide. Although this rate constant can only be taken as an upper limit of the reaction rate, this near identity with *n*-propyl bromide agrees best with the formulation as an S_N2 rate-determining step.

The similarity in the rates and activation energies between the reactions involving $[Ni(NiL_2)_2]Cl_2$ and $[Ni_2L_2]$, even though there is a difference in the

Table IV. Relative Rates, Activation Energies, and Frequency Factors for Alkylation of $[Ni\{Ni(NH_2CH_2CH_2S)_2\}_2]Cl_2$ at 25° C.

RX	k_{av}, *L./Mole/Min.*	k *Relative*	E_a, *Kcal./Mole*	A, *L./Mole/Min.*
CH_3I	8.59×10^{-2}	11.2	11.7	3.3×10^{7}
C_2H_5Br	3.53×10^{-4}	0.046		
C_2H_5I	3.13×10^{-3}	0.407		
n-C_3H_7Br	2.98×10^{-4}	0.039		
n-C_3H_7I	1.52×10^{-3}	0.198		
$C_6H_5CH_2Br$	5.40×10^{-1}	70.2	10.9	5.4×10^{6}
$C_6H_5CH_2Cl$	7.69×10^{-3}	1.00	13.7	8.5×10^{7}
p-$ClC_6H_4CH_2Cl$	7.34×10^{-3}	0.954	14.2	1.6×10^{8}
p-$NO_2C_6H_4CH_2Cl$	4.94×10^{-3}	0.642	15.5	9.9×10^{8}

solvent, suggests that the two processes are similar. The rates for $[Ni(NiL_2)_2]Cl_2$ are consistently slower than those of $[Ni_2L_2]$. The coordinating ability of methanol is greater than that of chloroform and might well decrease the accessibility of the complex to the alkyl halide, thus decreasing the rate. This simple agreement is complicated by the occurrence of a dissociative equilibrium for the complex, $[Ni(NiL_2)_2]Cl_2$. In both cases the reaction with benzyl bromide exhibits the largest rate constant and the minimum temperature dependence. The para substituent on benzyl chloride has a smaller effect for reactions with $[Ni(NiL_2)_2]Cl_2$ than that with $[Ni_2L_2]$.

An additional factor was found to influence the rate of reaction in the experiments involving tetrakis (β-mercaptoethylamine)trinickel(II) ion. The addition of nickel chloride retarded the process. Methanol was used as the solvent to demonstrate that the dependence was actually due to the presence of nickel ion and not an ionic strength effect. Magnesium chloride accelerates the rate slightly, while nickel ion greatly retards the rate of reaction. This effect was studied in greater detail, but solubility requirements necessitated the use of a water-methanol mixed solvent. A solution of 5.5*M* water in methanol was found to be satisfactory to obtain the necessary solubilities of complex and nickel chloride.

The nickel ion dependence for the reaction between $[Ni(NiL_2)_2]Cl_2$ and methyl iodide is such that a predissociation of the complex is suggested. The experimental rate law appropriate for this system is

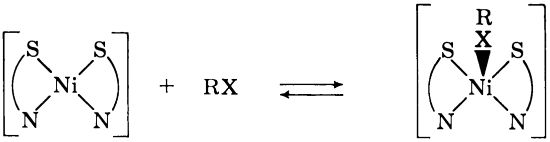
$$\text{Rate} = k(Ni_3L_4Cl_2)(RX)/(Ni^{+2})^{1/2} \qquad (21)$$

Furthermore, the apparent extinction coefficient for the complex increases steadily with increasing concentration of nickel chloride. On the basis of this evidence an attempt was made to determine the nature of the equilibrium involved and the extent to which dissociation takes place. Such an equilibrium has also been suggested by Jicha and Busch (*17*) on the basis of the results obtained from the method of continuous variations. The appropriate equilibrium appears to be that given in Equation 22.

$$Ni(NiL_2)_2^{+2} \rightleftharpoons Ni^{+2} + 2NiL_2 \qquad (22)$$

The equilibrium constant appears to be of the order of 10^{-7}. Consequently, it appears that the bis complex, NiL_2, is present in sufficient amounts to be the principal reactant in the reactions with alkyl halides.

On this basis, it appears that these two systems involving $[Ni_2\{CH_3N(CH_2CH_2S)_2\}_2]$ and $[Ni_3(NH_2CH_2CH_2S)_4]Cl_2$ have much in common. The terminal and not the bridged sulfur atoms are the ones at which the addition reaction takes place. The possibility exists of a pre-equilibrium of the type shown in Equation 23.



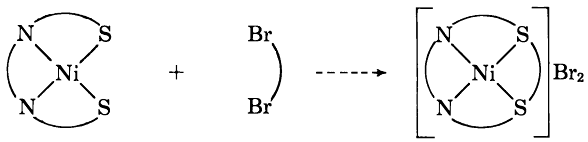
(23)

This concept may be used to rationalize the low values for the energies of activation in both cases.

The results obtained with $[Pd(NiL_2)_2]Cl_2$ are significant, even though the rate was too small to be determined. The fact that benzyl bromide merely reacted with solvent in this system reveals the relative magnitudes of the dissociative equilibria in the two systems$[Pd(NiL_2)_2]Cl_2$—RX and$[Ni(NiL_2)_2]Cl_2$—RX, for both produce $Ni(NH_2CH_2CH_2S)_2$ as the species which may react with the alkyl halide. The lesser dissociation of the palladium complex is totally expected. The fact that $NH_2CH_2CH_2SH$ reacts much more slowly with alkyl halides than the nickel complex supports the order of nucleophilicity of the coordinated sulfur atom. It will be useful to study other metal ion systems to extend this comparison.

Macrocyclization through Ligand Reactions of *cis*-Mercaptide Groups with Difunctional Alkylating Agents. Investigations summarized above have revealed the feasibility of addition reactions at the coordinated sulfur atom. Sulfur atoms linked to the metal atom in positions cis to each other may react with difunctional alkylating agents to form new chelate rings. Busch and Thompson (7) have applied these results to the closure of large organic rings through the medium of ligand reactions.

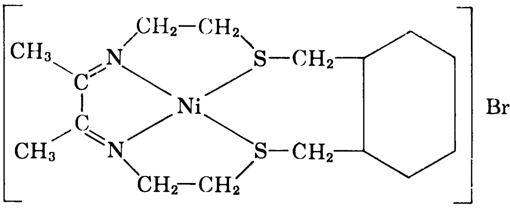
The family of complexes containing Schiff base ligands derived from α-diketones and β-mercaptoethylamine [the 2,2′-dialkyl(ethanediylidenedinitrilo)-diethanethiol complexes, structure V, Ni(BE), Ni(PE), and Ni(OE)] are well designed to extend chelate ring-forming ligand reactions to their ultimate by forming complete macrocycles, that completely enclose the metal ion. The objective is shown in Equation 24.



(24)

The susceptibility of the mercaptide groups in these Schiff base complexes to ligand reaction was evaluated by treating these compounds with methyl iodide and benzyl bromide in chloroform solution. The pure compounds isolated from these reaction mixtures were of the composition NiL.2RX, where L represents the tetradendate Schiff base and RX represents the alkyl halide added. These reactions proceed smoothly and the stoichiometry of the products implies that both sufur atoms are reactive. The products are monomeric in dichloroethane. They exhibit magnetic moments consistent with octahedral structures, and they behave as di-univalent electrolytes in coordinating, polar solvents.

Compounds were available to test the hypothesis that macrocyclization should be favored by ligand reactions of the type illustrated by Equation 24. The one remaining problem to be solved was that of the proper difunctional alkylating agent. Thompson and Busch (7) have found that the most convenient reagent is α,α′-dibromo-*o*-xylene. The reactions of Ni(BE) and Ni(PE) with α,α′-dibromo-*o*-xylene proceed rapidly in chloroform, yielding a soluble product that may be isolated by concentrating the solution. After recrystallization from ethanol and drying, the brown product conforms very closely to the composition required by structure VIII. The products, abbreviated as Ni(BEX)Br_2 and Ni(PEX)Br_2, are monomeric in dichloroethane and exhibit infrared spectra consistent with the assigned structure.



VIII

Similar experiments with the same complexes and trimethylene diiodide and with ethylene dibromide have not been equally satisfactory. However, the system involving trimethylene diiodide is promising. These results are consistent with the findings of studies of molecular models. α,α-Dibromo-*o*-xylene and trimethylene diiodide are well suited, in the steric sense, to the closing of the single remaining open side of the complex, while ethylene dibromide appears to be too short to span the open edge.

The success of these experiments provides a complete vindication of the suggestion that the coordination sphere of a metal ion represents the simplest and best understood chemical template, and that it may hold reactive groups in juxtaposition so that complicated multistep reactions may occur in a sterically highly selective manner. The specific examples cited provide a new principle of ring closure which has a counterpart in the synthesis of basketlike and cagelike structures.

Acknowledgment

The financial support of the National Institutes of Health is gratefully acknowledged.

Literature Cited

(1) Basolo, F., Pearson, R. G., "Mechanisms of Inorganic Reactions," p. 55, Wiley, New York, 1958.
(2) *Ibid.*, p. 122.
(3) Burke, J. A., Jr., Busch, D. H., Morris, M. L., unpublished results.
(4) Busch, D. H., ADVAN. CHEM. SER., No. **37**, 1 (1963).
(5) Busch, D. H., Findley, W. R., unpublished results.
(6) Busch, D. H., Jicha, D. C., *Inorg. Chem.* **1**, 884 (1962).
(7) Busch, D. H., Thompson, M. C., *Chem. Eng. News* **39**, 57 (Sept. 17, 1962).
(8) Ewens, R. G. V., Gibson, C. S., *J. Chem. Soc.* **1949**, 431.
(9) Felder, E., Paoli, E., Tiepolo, U., *Farmaco (Pavia), Ed. Sci.* **10**, 836 (1955).
(10) Felder, E., Radica, A. R., *Gazz. Chim. Ital.* **85**, 453 (1955).
(11) Frost, A. A., Pearson, R. G., "Kinetics and Mechanism," p. 49, Wiley, New York, 1953.
(12) Harley Mason, J., *J. Chem. Soc.* **1952**, 146.

(13) Ingold, C. K., "Structure and Mechanism in Organic Chemistry," p. 358, Cornell Univ. Press, Ithaca, N. Y., 1953.
(14) *Ibid.*, p. 408.
(15) Jensen, K. A., *Z. inorg. allgem. Chem.* **252**, 227 (1944).
(16) Jicha, D. C., Busch, D. H., *Inorg. Chem.* **1**, 872 (1962).
(17) *Ibid.*, p. 878.
(18) Jicha, D. C., Busch, D. H., Division of Inorganic Chemistry, 135th meeting, ACS, Boston, Mass., 1958.
(19) Kornblum, N., Blackwood, R. K., *J. Am. Chem. Soc.* **78**, 4037 (1956).
(20) Kornblum, N., Smiley, R. A., Blackwood, R. K., Iffland, D. G., *Ibid.*, **77**, 6269 (1958).
(21) Li, N. C., Manning, R. A., *Ibid.*, **77**, 5225 (1955).
(22) Streitweiser, A., *Chem. Revs.* **56**, 571 (1956).
(23) Thompson, M. C., Busch, D. H., *J. Am. Chem. Soc.* **84**, 1762 (1962).
(24) Wrathall, J. W., Hohne, R., Root, C. A., Busch, D. H., unpublished results.

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9

Reactivity of Hydroxyl Groups in the Bis(2-hydroxyethyliminodiacetato)chromium(III) Ion

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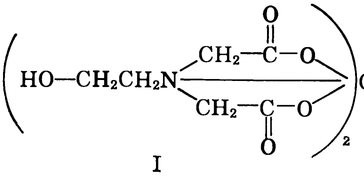
Several reactions, generally capable of acetylating alcohols, were attempted on the anionic complex $[Cr(HO\text{-}A)_2]^-$; most failed to acetylate the uncoordinated hydroxyl groups. Refluxing in a glacial acetic acid–acetic anhydride mixture led to extensive decomposition of the complex but produced a small quantity of the diester, $[Cr(AcO\text{-}A)_2]^-$, isolated as the water-insoluble oxonium salt, $(H_3O)\,[Cr(AcO\text{-}A)_2]$. The reaction of $(Me_4N)\,[Cr(HO\text{-}A)_2]$ with ketene in refluxing acetonitrile produced the diester; the ketene reaction, however, is unusually slow. It is concluded that charge on the complex molecule may not be an important factor governing attack on uncoordinated hydroxyl groups, and a mechanism for the ketene reaction is discussed.

The reactivity of a hydroxyl beta to a coordinated amino group has been the subject of several papers. Keller and Edwards (*4*) investigated tris(2-hydroxyethylethylenediamine)cobalt(III) chloride and found the uncoordinated hydroxyl group to be completely unreactive, even in refluxing acetyl chloride. Drinkard, Bauer, and Bailar (*1*) have re-examined this system more recently. They discuss the fact that the functional groups of the attacking molecules bear a partial positive charge; consequently, attack on a positively charged complex molecule should be unfavorable.

It was of interest to us to examine the problem of acetylation of an —OH group beta to a coordinated amino group in a complex molecule bearing a negative charge. The acetylation of the uncoordinated hydroxyl groups of the bis(2-hydroxyethyliminodiacetato)chromium(III) ion (I) is described below.



$[Cr(HO{-}A)_2]^-$

I

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Experimental

Preparation of K[Cr(HO-A)$_2$] and (Me$_4$N)[Cr(HO-A)$_2$]. A solution of 23.2 grams (0.36 mole) of KOH in water was added to an aqueous slurry of 42.5 grams (0.24 mole) of HO-AH$_2$. This was added to a solution of 31.9 grams (0.12 mole) of chromium(III) chloride 6-hydrate in water; the total volume of water used was 500 ml. After digestion on the hot plate for a few minutes, the dark red solution was neutralized to pH 7 (pH paper) using 7.76 grams (0.12 mole) of KOH in 20 ml. of water. The solution was filtered, evaporated on a steam bath to approximately 450 ml., and allowed to stand overnight. After the product had been isolated by filtration it was washed three times with water and dried in vacuo over P_2O_5. Yield: 34.5 grams. Evaporation of the filtrate to 200 ml. afforded an additional 9.5 grams of product.

The complex was recrystallized by dissolving 44.0 grams of the crude material in 150 ml. of hot water. After cooling, the product was isolated as a red crystalline solid in the same manner as above. Yield: 31.2 grams (58.9%). Calculated for [$KCrC_{12}H_{18}O_{10}N_2$]: C, 32.7; H, 4.12; N, 6.35; Cr, 11.8. Observed: C, 32.12, 31.99; H, 4.05, 4.40; N, 6.63; Cr, 10.9.

The tetramethylammonium salt, (Me$_4$N)[Cr(HO-A)$_2$], was prepared from the potassium salt by ion exchange on Amberlite IR-120 in the tetramethylammonium cycle. Calculated for [$CrC_{16}H_{30}O_{10}N_3$]: C, 40.4; H, 6.36; N, 8.84. Observed: C, 40.53; H, 6.39; N, 8.67.

Acetylation of K[Cr(HO-A)$_2$] in Glacial Acetic Acid. Four grams (0.00906 mole) of K[Cr(HO-A)$_2$] was refluxed in 200 ml. of glacial acetic acid and 300 ml. of acetic anhydride for 2 hours. Filtration afforded 1.68 grams of starting material; the filtrate was evaporated to a viscous brown oil (rotary evaporator, steam bath) and diluted with a solution of 3 ml. of concentrated nitric acid in 50 ml. of water. After standing overnight the pink, crystalline solid was isolated by filtration and dried in vacuo over P_2O_5. Yield: 0.63 gram (23.7% on basis of 2.32 grams of complex dissolved). Analysis: Calculated for (H_3O)[Cr(AcOA)$_2$]: C, 38.00; H, 4.96; N, 5.55. Observed: C, 37.65; H, 5.24; N, 5.35. The oxonium salt may be recrystallized by dissolving in the stoichiometric amount of aqueous potassium bicarbonate and reprecipitating by the addition of nitric acid.

Preparation of Ketene. Ketene was prepared by the pyrolysis of acetone using a generator identical to that described in the literature (3). The generator was calibrated for ketene yield by passing the effluent gas through standard sodium hydroxide.

Acetylation of (Me$_4$N)[Cr(HO-A)$_2$] with Ketene. Ten grams (0.0209 mole) of (Me$_4$N) [Cr(HO-A)$_2$] was mixed with 550 ml. of acetonitrile and refluxed. Through this refluxing mixture ketene was passed for 6 hours (0.159 mole per hour, or 0.955 mole). After refluxing for an additional 18 hours the solution was filtered (0.14 gram of starting material recovered) and then evaporated to dryness. The solid was redissolved in 100 ml. of water and 7 ml. of concentrated nitric acid was added. The pink precipitate which formed was isolated by filtration, washed with alcohol and ether, and then dried in vacuo over P_2O_5. Yield: 10.17 grams (95.8%). Analysis: Calculated for (H_3O) [Cr(AcO-A)$_2$]: C, 38.00; H, 4.96; N, 5.55. Observed: C, 36.45; H, 5.38; N, 5.41. Although the carbon analysis is not ideal, this compound appeared to be identical to the oxonium salt isolated above (appearance, infrared spectrum, and conversion to the potassium salt).

Conversion of (H_3O) [Cr(AcO-A)$_2$] to Potassium Salt. A solution containing 0.30 gram (0.003 mole) of potassium bicarbonate in 10 ml. of water was added to a slurry of 1.00 gram (0.00197 mole) of (H_3O)[Cr(AcO-A)$_2$] in 50 ml. of water. The addition of 800 ml. of absolute ethanol to the resulting solution caused a pink precipitate to form, which was isolated by filtration, washed with absolute ethanol and ether, and air-dried. Yield: 0.72 gram (69.8%). Analysis. Calculated for K[Cr(AcO-A)$_2$]: C, 36.53; H, 4.21; N, 5.33. Observed: C, 36.67; H, 4.57; N, 5.27.

Attempted Reaction of K[Cr(HO-A)$_2$] with Acetyl Chloride in Water. One gram (0.00227 mole) of K[Cr(HO-A)$_2$] was dissolved in 50 ml. of water and cooled to 4°C., and 0.29 gram of potassium hydroxide (0.0045 mole) was added.

To this solution was added 0.35 gram (0.0045 mole) of acetyl chloride in 10 ml. of chloroform. After stirring for 15 minutes the aqueous and organic phases were separated, the former concentrated to 10 ml., and the red, crystalline solid isolated by filtration, washed with water, and dried in vacuo over P_2O_5. Yield: 0.44 gram.

The filtrate was evaporated to dryness. Yield: 0.81 gram. Infrared examination of both fractions showed the absence of ester and confirmed the identity of the first fraction as starting material. The second fraction appeared to be starting material and potassium acetate.

Attempted Reaction of $K[Cr(HO\text{-}A)_2]$ with Benzoyl Chloride in Water. To a solution of 2.00 grams (0.00454 mole) of $K[Cr(HO\text{-}A)_2]$ in 200 ml. of water, cooled to 6° C., were added 12.8 grams of benzoyl chloride and a solution of 2.00 grams of potassium bicarbonate in 20 ml. of water. This mixture was stirred in an ice bath for 30 minutes and then for an additional hour out of the bath. The solution was acidified with concentrated nitric acid, and then filtered to remove benzoic acid. From the filtrate only starting material (infrared spectrum) and its decomposition products could be isolated.

Attempted Reaction of $K[Cr(HO\text{-}A)_2]$ with Acetyl Chloride. One gram of $K[Cr(HO\text{-}A)_2]$ and 50 ml. of acetyl chloride were placed in a flask and refluxed for 24 hours. At the end of this time $K[Cr(HO\text{-}A)_2]$ was recovered unchanged (infrared spectrum); the liquid phase was colorless, indicating insolubility of the complex.

Attempted Reaction of $K[Cr(HO\text{-}A)_2]$ with Acetyl Chloride in DMF. One gram (0.00226 mole) of $K[Cr(HO\text{-}A_2]$ was mixed with 150 ml. of hot DMF and 1 ml. (excess) of acetyl chloride was added. The solution turned blue within 1 minute and within 30 minutes all solid appeared to have dissolved. After standing overnight the solution was evaporated to a green oil which gave no indication of the presence of ester (infrared spectrum).

Attempted Reaction of (Me_4N) $[Cr(HO\text{-}A_2]$ with Acetyl Chloride in Acetonitrile. In 200 ml. of acetonitrile were placed 0.50 gram (0.00105 mole) of (Me_4N) $[Cr(HO\text{-}A)_2]$, 1 ml. of pyridine, and 18 drops (excess) of acetyl chloride. The solution was warmed and within a few minutes the color changed from red to green. On evaporation a green oil was obtained, the infrared spectrum of which gave no indication of the presence of ester.

Attempted Reaction of $K[Cr(HO\text{-}A)_2]$ with Acetic Acid. Two grams (0.00454 mole) of $K[Cr(HO\text{-}A)_2]$ was dissolved in 150 ml. of glacial acetic acid and refluxed, slowly distilling solvent. After several hours of such treatment the solution was allowed to stand overnight and then evaporated to a viscous, blue oil. By dissolving this in water and collecting fractions as the aqueous solution was evaporated, all starting material was recovered unchanged (identified by its infrared spectrum).

Attempted Reaction of $(Me_4N)[Cr(HO\text{-}A)_2]$ with Acetic Anhydride in Acetonitrile. Seven-tenths gram (0.00147 mole) of $(Me_4N)[Cr(HO\text{-}A)_2]$ was mixed with 250 ml. of acetonitrile and 1 ml. (0.009 mole) of acetic anhydride. After refluxing for 1 hour a small quantity of starting material was recovered by filtration and the solution was concentrated to 15 ml. The solid which crystallized was isolated by filtration, washed with acetonitrile and ether, and air-dried. Infrared examination proved this compound to be starting material.

Reactions of $[Cr(AcO\text{-}A)_2]^-$. Two grams of (H_3O) $[Cr(AcO\text{-}A)_2]$ (freshly reprecipitated) was mixed with 15 to 25 ml. of solvent and refluxed for ca. 4 hours. Some solvent was removed by distillation and examined by means of vapor phase chromatography for a new component. The results are summarized below:

Solvent	*New Component in Distillate*
Methanol	Methyl acetate
Ethanol	Ethyl acetate
Ethyl propionate	Ethyl acetate

The complexes were not isolated from these reactions.

When 1.5 grams of $K[Cr(AcO\text{-}A)_2]$ was refluxed with 15 ml. of absolute ethanol for 4 hours no new components could be detected in the distillate by means of vapor phase chromatography.

Vapor Phase Chromatography. VPC data were obtained on a Perkin Elmer Vapor Fractometer, Model 154D, using an 0 column on Celite, at 15 pounds of helium pressure. The temperature was varied depending on the components to be separated, but was ca. 92°. In each experiment a mixture of knowns was run for comparison purposes.

Infrared Spectra. Infrared spectra were obtained on a Perkin Elmer Model 21 spectrophotometer using mineral oil and halocarbon mulls.

Discussion

Several attempts to prepare typical alcohol derivatives of $[Cr(HO\text{-}A)_2]^-$ were unsuccessful; these include Schotten-Bauman conditions (acetyl chloride in chloroform shaken with cold, aqueous alkaline solution of complex), refluxing in acetyl chloride, in glacial acetic acid, acetyl chloride in hot dimethyl formamide, acetyl chloride and pyridine in acetonitrile, and acetic anhydride in acetonitrile. The failure of refluxing acetyl chloride to effect acetylation brings to mind the work of Keller and Edwards (*4*); the acetyl chloride system is completely heterogeneous and consequently not conducive to reaction. However, even the homogeneous reaction of $[Cr(HO\text{-}A)_2]^-$ with acetyl chloride in acetonitrile failed to give a measurable quantity of the diester.

Although refluxing in glacial acetic acid failed to acetylate the complex, using a solvent of glacial acetic acid–acetic anhydride led to the formation of a low yield of the diester. This compound was isolated as the water-insoluble oxonium salt, $(H_3O)[Cr(AcO\text{-}A)_2]$. The insolubility of this salt in water was surprising; examination of its infrared spectrum shows the asymmetric carboxyl stretching mode (at 1630 cm.$^{-1}$) to be ca. 20 cm.$^{-1}$ lower than that in the corresponding tetramethylammonium salt. This indicates an interaction between coordinated carboxyl and H_3O^+, and is probably the cause of the insolubility of (H_3O) $[Cr(AcO\text{-}A)_2]$.

On heating, glacial acetic acid solutions of $[Cr(HO\text{-}A)_2]^-$ change color to dark blue; this color change probably indicates ligand displacement, according to

$$[Cr(HO\text{-}A)_2]^- + 3\ HOAc \rightarrow [Cr(HO\text{-}A)(OAc)_3]^{-2} + HO\text{-}AH_3^+$$

Free ligand could undergo acetylation, recoordinate, and give the diester which was isolated. This system may not involve a ligand reaction. Refluxing free ligand with acetic acid–acetic anhydride gives a brown oil similar to that obtained in these experiments involving the complex.

Consequently, it was deemed desirable to operate in a very weakly coordinating solvent if possible. Since acetonitrile is a much poorer donor solvent than glacial acetic acid, and since the tetramethylammonium salt of the chromium(III) complex is soluble in acetonitrile, this appeared to be an ideal solvent for running ligand reactions. However, initial experiments indicated that neither acetic anhydride nor acetyl chloride would acetylate the complex in this solvent.

Ketene is known to be a very active acetylating agent. This reagent reacted with the complex, $[(CH_3)_4N]$ $[Cr(HO\text{-}A)_2]$, in acetonitrile solution to produce the diester. However, ketene, which normally reacts with alcohols very quickly, reacted slowly in this case (Table I). In all ketene reactions a large excess of ketene was passed through the solution; the critical factor determining yield appears to be the total time of refluxing.

Because of the reaction conditions employed (poor donor solvent, absence of nucleophilic reagents for ligand displacement) it seems certain that a ligand reaction is occurring in this system, and not acetylation of displaced ligand as is probable in the acetic acid–acetic anhydride system.

Table I. Reaction of $(Me_4N)[Cr(HO\text{-}A)_2]$ with Ketene

$$[Cr(HO\text{-}A)_2]^- + 2\ CH_2{=}C{=}O \rightarrow [Cr(AcO\text{-}A)_2]^-$$

Equiv. Ketene[a]/ Equiv. Complex	*Reflux Time, Hours*	*Yield, %*
31.6	2 1/2	18
47.4	3 3/4	35
75.9	24	91
75.9	24	83

[a] In all experiments 3.0 grams of complex was dissolved in 550 ml. of refluxing acetonitrile.

Because of the difficulty encountered in acetylation of the complexed alcohol, it was of interest to see if the ester complex behaves in a normal fashion. Refluxing $(H_3O)[Cr(AcO\text{-}A)_2]$ in methanol or ethanol caused methyl or ethyl acetate to be formed, while refluxing in ethyl propionate formed ethyl acetate. When the potassium salt was used in place of the oxonium salt no transesterification was observed; this could be due to the necessity of acid catalysis or a difference in solubility in these essentially heterogeneous systems. The oxonium salt, $(H_3O)[Cr(AcO\text{-}A)_2]$, appears to have typical ester reactivity.

The structure of the "alcohol" complex, $[Cr(HO\text{-}A)_2]^-$, has been elucidated by means of infrared spectra (5); one asymmetric carboxyl stretching mode near 1650 cm.$^{-1}$ implies that all four carboxyl groups are equivalent and coordinated. Coordination of the two nitrogen atoms then satisfies the hexa-coordinate requirement of chromium(III), dictating that the alcohol group must remain uncoordinated; the OH stretching mode for these groups at 3380 and 3300 cm.$^{-1}$ is in the region for uncoordinated hydroxyls. In the ester, $[Cr(AcO\text{-}A)_2]^-$, the absence of absorption in the 3400-cm.$^{-1}$ region indicates the loss of alcohol groups, while the new band at 1740 cm.$^{-1}$ verifies the presence of ester. One asymmetric carboxyl stretching mode, again in the 1650-cm.$^{-1}$ region, substantiates the belief that the coordination sphere remains unchanged (Table II). Further verification of the identity of the coordination spheres in $[Cr(HO\text{-}A)_2]^-$ and $[Cr(AcO\text{-}A)_2]^-$ is found in the fact that the visible-ultraviolet absorption spectra of these compounds are nearly identical ($K[Cr(HO\text{-}A)_2]$ $\lambda_{max.}$ 516 (ϵ 43.7), 365 (ϵ 31.5); $K[Cr(AcO\text{-}A)_2]$ $\lambda_{max.}$ 506 (ϵ 46.1), 358 (ϵ 36.8)). If the former compound involved coordination of the alcohol groups, one would expect a greater shift in the spectrum than that which is observed.

Table II. Infrared Spectra in the 4000- to 1500-Cm.$^{-1}$ Region

Assignment	(H_3O) $[Cr(AcO\text{-}A)_2]$	$K[Cr(AcO\text{-}A)_2]$	$K[Cr(HO\text{-}A)_2]$	$(CH_3)_4N$- $[Cr(HO\text{-}A)_2]$
OH stretch			3380 m	3380 m
			3300 m	
H_3O^+	3100 vb, w			
				3040 w
	2980 w	2980 w	2940 w	2950 w
	2960 w	2960 w		
—COOR	1735 s	1740 s		
	1660 sh	1695 sh		1695 sh
	1645 sh	1675 sh		
$—COO^-$ (asymm.)	1620 s	1660 s	1650 s	1665 s
		1650 s	1630 s	1645 s

vb, very broad; s, strong; m, medium; w, weak; sh, shoulder.

If charge on the complex molecule were an important factor in acetylating uncoordinated hydroxyl groups, one would expect anionic species to react rapidly.

The present work seems to indicate that charge on the molecule is not an important consideration from the standpoint of alcohol reactivity; electrolyte nature has a large effect on solubility, of course, and from this standpoint could affect reactivity. Choline salts [$(CH_3)_3\overset{+}{N}CH_2CH_2OH$] are readily acylated. Here the positive charge undoubtedly contributes to hydrolytic instability of the ester (2), but the alcohol ion is readily acylated. Apparently more than charge is involved in the reactivity of the uncoordinated hydroxyl groups in $[Cr(HO\text{-}A)_2]^-$.

The slow acetylation of the hydroxyl group is difficult to explain. One is inclined to suggest that this group is coordinated to the metal ion and consequently rendered inactive. Such a possibility requires either a coordination number of 7 for chromium(III) or displacement of carboxylate from the coordination sphere by hydroxyl. In the latter instance an uncoordinated functional group would still be present to react with ketene (COO^- or COOH) and anhydride should be detected in the crude reaction product. This is not the case.

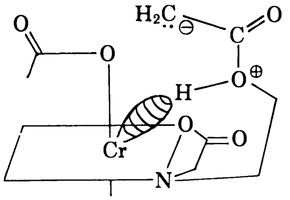
A coordination number of 7 does not seem likely for chromium(III); also, the infrared spectrum indicates that this compound contains uncoordinated hydroxyl groups. The similarity of the visible-ultraviolet absorption spectra of $[Cr(HO\text{-}A)_2]^-$ and $[Cr(AcO\text{-}A)_2]^-$ (above) is further evidence of the identical character of the donor groups in both compounds, and hence, hydroxyl groups appear to be uncoordinated in the former. We must seek an explanation not involving coordination of the hydroxyl oxygen to chromium(III).

Another effect to be considered is an inductive effect; although the total charge on the complex molecule, $[Cr(HO\text{-}A)_2]^-$, is negative, it is possible that chromium(III) exerts its effect on the free OH group, increasing the acidity of the alcohol proton. "Acidic" alcohols, such as phenol, may be acetylated readily, so that this does not seem to be a plausible explanation for the very slow ketene reaction.

Interaction of the alcohol groups with solvent must also be considered. Some form of solvent interaction does not appear to be a good explanation when one considers the wide variety of solvents investigated for acetylation of this compound; water, dimethyl formamide, glacial acetic acid, acetonitrile, and acetyl chloride (in a hetrogeneous system) were all employed with (or as) acetylating agents. It is difficult to compare our results in these various media, since different acetylating agents were used, but our lack of success in a number of different systems indicates that perhaps the same effect is operating in all of them. Any explanation for this observed lack of reactivity should account for the observations in all of these systems.

Steric hindrance does not, at first, seem to be a possible cause of the relatively slow rate of reaction. Molecular models indicate the $HOCH_2CH_2$ group to be free of the remainder of the molecule, and presumably available for acetylation.

One difference between the readily acylated choline ion and $[Cr(HO\text{-}A)_2]^-$ is that the latter has nonbonding *d*-orbitals containing electrons. If the alcohol proton were to hydrogen-bond to one of these orbitals, the steric availability of the oxygen would not be lowered and its nucleophilic character should be enhanced, contrary to our observation. The proton, however, might be only difficultly accessible in a transition state. If the alcohol proton were located in the face of the octahedron (by forming a hydrogen bond to a nonbonding *d*-orbital) it could be shielded by the donor groups at the octahedron apexes (II). This transition state could decompose to give ketene and the starting complex, or,



II

more slowly, the ester. A reaction involving a transition state of this sort might be greatly facilitated by the presence of a proton catalyst.

A principal objection to this mechanism is the requirement of a hydrogen bond to a nonbonding *d*-electron. Also, it does not explain the lack of reactivity with acetylating agents where no proton transfer is required—e.g., acetyl chloride and acetic acid. Unfortunately, this interesting phenomenon of extremely slow reactivity remains unexplained.

Acknowledgment

The authors thank their colleagues in the Chemical Research Department at Stamford for many stimulating discussions during the course of this work. They thank Daryle H. Busch for suggesting the possibility that the alcohol proton may hydrogen-bond to a *d*-orbital.

Literature Cited

(1) Drinkard, W. C., Bauer, H. F., Bailar, J. C., Jr., *J. Am. Chem. Soc.* 74, 215 (1952).
(2) Freese, C., *Ciencia* (*Mex.*) **13**, 143 (1953).
(3) Hanford, W. E., Sauer, J. S., *Org. Reactions* **3**, 132 (1946).
(4) Keller, R. N., Edwards, L. J., *J. Am. Chem. Soc.* 74, 215 (1952).
(5) Krause, R. A., unpublished manuscript.

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10

Phosphorus-Fluorine Chemistry.

II. Coordination Compounds of Zerovalent Nickel and Molybdenum with Fluorine-Containing Phosphine Ligands

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The reaction of potassium fluorosulfinate with chlorophosphines, R_nPCl_{3-n}, instead of the expected fluorophosphines, R_nPF_{3-n}, gave fluorides of phosphonic or phosphinic acids. Fluorophosphine complexes of zerovalent nickel were readily obtained upon fluorination of the corresponding complexes containing chlorophosphines coordinated to the metal, the latter being easily accessible. Interaction of chlorophosphines with group V trifluorides, such as AsF_3 or SbF_3, normally led to fluorophosphoranes, R_nPF_{5-n}, by a simultaneous redox and fluorination reaction. Chloromethyldichlorophosphine, however, was converted smoothly into the flammable fluorophosphine, which upon reaction with cycloheptatriene molybdenum tricarbonyl gave the corresponding trisdifluorophosphine–molybdenum tricarbonyl complex as a stable, distillable liquid.

In 1955, Seel and coworkers (*26, 27*) reported the addition of sulfur dioxide to alkali fluorides. X-ray studies on these sulfur dioxide adducts, which exhibited considerable thermal stability, revealed the fluoride ion to be bonded to a large extent to the sulfur dioxide with formation of a novel anionic species, the fluorosulfinate, SO_2F^-, ion. Potassium fluorosulfinate, $K^+SO_2F^-$, for instance, was shown to be closely related to the isoelectronic chlorate, $K^+ClO_3^-$. The potassium salt and its alkali homologs were found to react smoothly with covalent halogen compounds with sufficiently polar halogen atoms, according to

$$\text{R-Hal} + \text{MeSO}_2\text{F} \rightarrow \text{R-F} + \text{SO}_2 + \text{MeHal}$$

The behavior of the fluorosulfinate as an activated alkali fluoride is readily explained in terms of a widening of the fluoride crystal lattice, and the amount of energy required for its breakdown in fluorinations is accordingly lower.

A wide variety of fluorine compounds, both known and novel, could be obtained by means of the new fluorinating agent–cf., for instance (*21*)–and detailed studies of the scope and limits of its applications were undertaken.

In the course of these investigations the behavior of phosphorus-chlorine compounds appeared interesting, and it was found that potassium fluorosulfinate could be utilized in the straightforward synthesis of phosphorus fluorides, such as phosphorus trifluoride, phosphorus oxyfluoride, phosphorus thiotrifluoride, and certain organic derivatives of the latter two (*21, 23, 24, 26, 27*). Another interesting example was the first synthesis of the phosphonitrilic fluorides, $(PNF_2)_{3,4}$ (*28, 29*). In general, potassium fluorosulfinate turned out to be one of the better fluorinating agents in phosphorus-fluorine chemistry.

Organic derivatives of phosphorus trichloride—i.e., chlorophosphines of the types $RPCl_2$ or R_2PCl—had never been fluorinated. We assumed the hitherto unknown fluorophosphines to be possibly interesting ligands in coordination chemistry. Such expectations were supported by earlier observations of Chatt (*5, 6*) and Wilkinson (*32*), who found that the parent compound phosphorus trifluoride as a ligand in certain coordination compounds with platinum or nickel behaved very much like carbon monoxide.

Phenyldichlorophosphine was fluorinated first with potassium fluorosulfinate in benzene and was found to react readily with much evolution of heat. An apparently homogeneous product, having a sharp boiling point, was isolated, but was identified as a constant boiling mixture of the phosphonic difluorides, $C_6H_5POF_2$ and $C_6H_5PSF_2$, respectively. The elements of sulfur dioxide, which always accompanies fluorination reactions with potassium fluorosulfinate, added to the apparently strongly reducing fluorophosphine, according to the following equation:

$$3C_6H_5PCl_2 + 6KSO_2F \rightarrow 2C_6H_5POF_2 + C_6H_5PSF_2 + 5SO_2 + 6KCl$$

The pure phosphonic difluorides, also unknown at the time of our investigation, were subsequently synthesized (*23, 24*) and found to have almost identical boiling points, as is common with other organic phosphorus compounds, containing P=O or P=S bonds, respectively (*13*). Because of the polarity of the P=O groups, the P=O compounds appear to be considerably associated. This effect is even more striking in the case of methyldichlorophosphine, which upon reaction with potassium fluorosulfinate under conditions similar to those used with the phenyl compound, was converted into methylphosphonothioic difluoride (b.p. 60°) and methylphosphonic difluoride (b.p. 99°) (*21*), the P=O compound boiling almost 40° higher than the corresponding thiono compound. Again, the reaction products were finally identified by the independent synthesis of methylphosphonothioic difluoride and methylphosphonic difluoride (*21, 24*), the latter together with a few methyl alkyl phosphinic fluorides, $CH_3(R)POF$ (*7*), being the only previously known phosphonic and phosphinic acid fluorides.

As in the above examples, where a search for the fluorophosphines, even under carefully controlled reaction conditions, proved unsuccessful, the secondary chlorophosphine, dimethylmonochlorophosphine, did not give the fluorophosphine $(CH_3)_2PF$, claimed as a product of its reaction with potassium fluorosulfinate, in the absence of physical or experimental data (*26*). The corresponding phosphinic fluorides, resulting from the addition of sulfur and oxygen to the trivalent phosphorus, were obtained instead. The product, which has a narrow boiling range, was identified as a mixture by infrared and gas chromatographic comparison with the independently prepared authentic compounds (*21*).

It must be concluded, therefore, that fluorophosphines are strongly reducing, a fact which was confirmed in further attempts at their preparation, using different reagents in the fluorination of chlorophosphines. There was either no reaction at all under the experimental conditions—e.g., with alkali fluorides in benzene as a solvent—or the trivalent phosphorus in the starting chlorophosphine was readily converted to the quinquevalent state—e.g., when phenyldichlorophosphine reacted with sodium fluoride in the presence of an antimony trioxide catalyst in a polar solvent such as acetonitrile to give phenylphosphonic difluoride. Recent Russian work showed that phenyldichlorophosphine was converted into phenyltetrafluorophosphorane, $C_6H_5PF_4$, when it reacted with antimony trifluoride (*34*),

$$3C_6H_5PCl_2 + 4SbF_3 \rightarrow 3C_6H_5PF_4 + 2Sb + 2SbCl_3$$

while another recent Russian paper described for the first time the preparation of a few fluorophosphines in low yield on interaction of chlorophosphines with antimony trifluoride under mild conditions (*15*). These compounds actually were found to be spontaneously flammable in the atmosphere. We have studied the above-mentioned redox reaction extensively (*22*) and found it to be of very general scope and highly useful in the facile synthesis of fluorophosphoranes, RPF_4 and R_2PF_3, from chlorophosphines, $RPCl_2$ or R_2PCl, when arsenic trifluoride or antimony trifluoride is employed as fluorinating agent. Among some 20 examples studied we found but one exception—chloromethyldichlorophosphine, $ClCH_2PCl_2$, which on interaction with antimony trifluoride did not undergo the usual redox reaction with formation of the fluorophosphorane, but was converted into the fluorophosphine, a volatile, spontaneously flammable liquid, a coordination compound of which is described.

Results and Discussion

Knowing all these facts, especially the difficult access to fluorophosphines and the poor donating abilities of phosphorus trifluoride (*5*, *6*), we decided to use another approach, which readily led to a number of coordination compounds with fluorophosphine ligands—namely, the fluorination of chlorophosphines already coordinated to the transition metal, where the 3*s* electrons of phosphorus are blocked by the complex formation. There was no reaction between elemental nickel and phosphorus trifluoride, even under extreme conditions, whereas the exchange of carbon monoxide in nickel carbonyl upon interaction with phosphorus trifluoride proceeded very slowly and even after 100 hours' interaction did not lead to a well defined product (*5*, *6*).

At the time of our investigation the only known coordination compounds of chlorophosphines (aside from phosphorus trichloride complexes) were the nickel-(0) compounds, tetrakis(methyldichlorophosphine)nickel-(0) (*20*) and tetrakisphenyldichlorophosphine)nickel-(0) (*17*). Tetrakis(methyldichlorophosphine)-nickel-(0) is noteworthy in that it represents a still rare example of the direct reaction of a ligand with an elemental transition metal to give a complex, while tetrakis(phenyldichlorophosphine)nickel-(0), like tetrakis(trichlorophosphine)-nickel-(0), was obtained readily via the carbonyl. All chlorophosphine-nickel-(0) complexes, including the phosphorus trichloride complex, $Ni(PCl_3)_4$, are compounds relatively stable in the atmosphere, but show poor stability in almost any organic solvent, even under strictly anaerobic conditions.

In our study of the fluorination of coordinated chlorophosphine ligands (*23*), we started out with tetrakis(trichlorophosphine)nickel-(0), which could previously be converted into tetrakis(trifluorophosphine)nickel-(0) by displacement of the coordinated phosphorus trichloride with excess phosphorus trifluoride in a sealed tube (*32*). The limitations of this method, requiring the use of phosphorus trifluoride, a low boiling gas, under pressure, and involving the mechanical separation of the fluorophosphine complex from phosphorus trichloride, are obvious, and the yield was low. A straightforward method for the synthesis of this interesting compound was found in the fluorination of the coordinated phosphorus trichloride with potassium fluorosulfinate:

$$Ni(PCl_3)_4 + 12KSO_2F \rightarrow Ni(PF_3)_4 + 12KCl + 12SO_2$$

There was a mildly exothermic reaction starting at room temperature when tetrakis(trichlorophosphine)nickel-(0), dissolved in *o*-dichlorobenzene as a high-boiling solvent, was stirred with potassium fluorosulfinate. The reaction was brought to completion by gentle heating for 1 to 2 hours, during which period most of the volatile product was condensed together with the sulfur dioxide. Tetrakis(trifluorophosphine)nickel-(0) was not miscible with sulfur dioxide and formed the lower layer. The final purification by distillation at atmospheric pressure, possible with very little decomposition, gave the complex as a colorless liquid boiling at 70.5° at atmospheric pressure, the yield ranging between 20 and 35%. Analytical and vapor pressure data (*23*) showed close agreement with the results of Wilkinson (*32*).

Attempts to effect fluorination of tetrakis(trichlorophosphine)nickel-(0) using benzoylfluoride as a fluorinating agent were also successful, tetrakis(trifluorophosphine)nickel-(0) and partially fluorinated liquid intermediates being isolated (*23*). The eutectic mixture potassium fluoride–hydrogen fluoride of the composition KF.3HF, on the other hand, showed no interaction with tetrakis(trichlorophosphine)nickel-(0) up to the decomposition temperature of the latter.

Using the potassium fluorosulfinate method further fluorophosphine-nickel-(0) complexes could be prepared (*23*), according to:

$$Ni(CH_3PCl_2)_4 + 8KSO_2F \rightarrow Ni(CH_3PF_2)_4 + 8SO_2 + 8KCl$$

$$Ni(C_6H_5PCl_2)_4 + 8KSO_2F \rightarrow Ni(C_6H_5PF_2)_4 + 8SO_2 + 8KCl$$

Both compounds being colorless and volatile, the liquid methyl derivative could be distilled in vacuo (b.p. 66–68° at 3.5 mm.), while the phenyl compound is a crystalline solid melting at 66°, which is sublimable in vacuo. The fluorination reactions occur somewhat less vigorously than in the case of the phosphorus trichloride nickel-(0) complex, and gentle heating was normally required to initiate the reaction. Benzene was used as a solvent.

Tetrakis(phenyldifluorophosphine)nickel-(0) could also be obtained, using arsenic trifluoride in the presence of catalytic amounts of antimony pentachloride, or zinc fluoride as fluorinating agents. Yields as high as 50% could be obtained, but sizable decomposition on the process of fluorination of the chlorophosphine nickel-(0) complexes in solution could not be entirely suppressed. The marked instability of zerovalent nickel-phosphine complexes in solution in organic solvents, even under strictly anhydrous and anaerobic conditions, has been noted by several workers (*16, 20*), but is still lacking a detailed explanation. A closer examination of the system carbon tetrachloride–tetrakis(trichlorophosphine)nickel-(0) (*23*) showed the main path of the reaction to consist in the formation of hexachloroethane with conversion of zerovalent into bivalent nickel, while the coordinated phosphorus trichloride was released. Instability in solution, although to a much lesser extent, was also noted for the fluorophosphine complexes, which are markedly hydrophobic. Tetrakis(trifluorophosphine)nickel-(0) can even be steam-distilled with only moderate thermal decomposition (*32*).

The comparatively simple method of preparation of tetrakis(trifluorophosphine)nickel-(0) encouraged some scouting experiments on its still unexplored chemistry. Whereas the compound is hydrolytically remarkably stable, it was found to react readily with amines and ammonia with complete aminolysis of the phosphorus-fluorine bonds. Very typical of tetrakis(trifluorophosphine)nickel-(0) and similar fluorophosphine and chlorophosphine complexes of zerovalent nickel is the rapid decomposition with precipitation of elemental nickel by aqueous alkali hydroxide.

It was decided to study the system tetrakis(trifluorophosphine)nickel-(0)–ammonia (*23*) in some detail; a smooth reaction was observed when the complex, condensed on excess ammonia at liquid air temperature, was allowed to warm up gradually. Precipitation of colorless crystals, identified as ammonium fluoride in almost stoichiometric amount, based on complete ammonolysis of the phosphorus-fluorine bonds, was observed at temperatures as low as −90° to −80°. Removal of the ammonium fluoride by filtration at temperatures not higher than −50°, and subsequent slow evaporation of the ammonia from the filtrate invariably led to a brown-yellow solid, although a colorless, crystalline material was formed initially. The product was decomposed almost instantaneously by water with precipitation of elemental nickel. Analysis of the hydrolyzate obtained in aqueous hydrochloric acid revealed a nickel-phosphorus-nitrogen atom ratio close to 1:4:4, corresponding to an apparently polymeric condensation product.

Thus, a stable derivative of phosphorus triamide, $P(NH_2)_3$, could not be obtained. Such expectations were encouraged by recent work of Kodama and Parry (*12*), who succeeded in ammonolyzing phosphorus trifluoride–borane, $F_3P.BH_3$, with formation of a stable phosphorus triamide–borane, $(H_2N)_3P.BH_3$. Ammonolysis of boron- or phosphorus-fluorine rather than -chlorine bonds is advantageous, since ammonium fluoride is insoluble in liquid ammonia and can easily be separated, while ammonium chloride is readily soluble.

Another interesting consideration was the possibility of complexes of zerovalent nickel with phosphine, PH_3, as a ligand. According to the scant information available, nickel carbonyl reacted with phosphine to give a nickel phosphide, NiP (*9*), and the expectations of preparing a coordination compound appeared discouraging. An attempt to convert coordinated phosphorus(III)-halide ligands into the hydride employing complex metal hydrides had not been made and, therefore, seemed worthwhile.

Tetrakis(trifluorophosphine)nickel-(0) interacted with sodium borohydride in water and diglyme as well as tetrakis(trichlorophosphine)nickel-(0) with lithium aluminum hydride at −80°. Rapid decomposition was noted in every case, and phosphine was the only identified product, no indication of a coordination compound with phosphine as a ligand being found. It may be assumed that zerovalent nickel-phosphine complexes are too unstable to be isolated; this conclusion is further supported by an experiment involving the reaction of nickel carbonyl with an organophosphorus hydride, phenylphosphine. Exchange of carbon monoxide proceeded rapidly at room temperature, and there was a sharp limit in stability after replacement of two CO groups, the conditions for the isolation of the dicarbonyl-bis(phenylphosphine)nickel-(0) complex being critical. The product in a pure state was a colorless, extremely air-sensitive solid, which decomposed rapidly above ca. 60°. Tetrakis(organophosphine)nickel-(0) complexes may be accessible via the reaction of chlorophosphine complexes of the type Ni$(RPCl_2)_4$ with metal hydrides, but no further attempts in this direction were undertaken.

The instability of transition metal–phosphine complexes has been discussed by Orgel (*18*) in terms of the great mobility of the hydrogen atoms, which allows secondary transformations to occur which would be impossible in substituted phosphine. Furthermore, the basicities of unsubstituted and substituted phosphine are expected to be different, presumably because of the difference in bond angle, requiring a larger amount of energy to enable phosphine to reorganize for the formation of tetrahedrally oriented bonds. The comparable ease of coordination of substituted phosphine is readily explained by the originally greater C-P-C bond angle.

In the course of a study of the formation of fluorophosphoranes from chlorophosphines (*22*) we observed one exception in the compound chloromethyldichlorophosphine, which reacted smoothly with antimony trifluoride to give the flammable fluorophosphine, $ClCH_2PF_2$, under conditions where many other chlorophosphines were invariably converted into fluorophosphoranes. As this fluorophosphine is readily available, its interaction with a metal carbonyl derivative was studied, and cycloheptatriene molybdenum tricarbonyl, obtained from the reaction of molybdenum hexacarbonyl with cycloheptatriene (*1*, *2*), was chosen as a starting compound.

In an inert atmosphere, excess chloromethyldifluorophosphine was distilled on cycloheptatriene molybdenum tricarbonyl, and the hydrocarbon ligand was readily displaced in a mildly exothermic reaction, requiring a reaction time of as little as 20 to 30 minutes. A high boiling colorless liquid (b.p. 127° at 0.05 mm.) was isolated by distillation, which could be shown to be the expected molybdenum tricarbonyl derivative, formed according to:

$$C_7H_8Mo(CO)_3 + 3ClCH_2PF_2 \rightarrow (ClCH_2PF_2)_3Mo(CO)_3 + C_7H_8$$

The product probably represents the first liquid, distillable coordination compound of zerovalent molybdenum, noteworthy also for its stability in the atmosphere.

Characterization of the fluorophosphine complexes included the determination of their infrared spectra. Tetrakis-(trifluorophosphine)nickel-(0), for instance, was found to have a very simple infrared spectrum (*23*) with the P-F stretching frequencies in the 850- to 900-cm.$^{-1}$ region, virtually unchanged as compared with uncoordinated phosphorus trifluoride (*10*). To permit a possible assignment of P-F absorptions in the organofluorophosphine–nickel-(0) complexes, the infrared spectra of the latter and of the uncoordinated and coordinated chlorophosphines were compared. The absorptions due to the organic groups were generally shifted very little, the differences being largely attributable to the different aggregation state of the samples. In tetrakis(methyldifluorophosphine)nickel-(0) strong absorptions at 781 and 723 cm.$^{-1}$ were assigned to P-F stretching frequencies, whereas a broad absorption at 790 cm.$^{-1}$ in tetrakis(phenyldifluorophosphine)-nickel-(0) could be assigned with certainty to P-F stretching.

The tris(chloromethyldifluorophosphine)molybdenum tricarbonyl exhibited strong CO absorptions typical for terminal CO groups at 2038 and 1970 cm.$^{-1}$. Strong P-F absorptions were found at 866 and 842 cm.$^{-1}$, which in view of the above-mentioned observation in the case of tetrakis(trifluorophosphine)nickel-(0) may also be representative of the uncoordinated fluorophosphine. Compared with molybdenum tricarbonyl derivatives with nitrogen compounds as donor molecules, a marked increase of the CO frequencies in the phosphine-substituted carbonyl is evident, which may be attributed to the π-character of the metal-ligand bond in the phosphine complexes, enhanced by the electronegativity of the fluorine atoms on the phosphorus.

As to the mode of formation and nature of bonding in fluorophosphine complexes, unsubstituted phosphorus trifluoride is a poor donor molecule, because of the presence of three fluorine atoms. Chloromethyldifluorophosphine (and presumably the other fluorophosphines) apparently possesses sufficient basic character to enable it to replace other ligands, bonded to transition metals. The strongly reducing character causing flammability in the atmosphere is not restricted to organofluorophosphines, but is also present in the parent compound, phosphorus trifluoride, which in a mixture with oxygen can react explosively when ignited by an electric spark, the enthalpy change, ΔH, for

$$PF_3 + {}^1/_2O_2 \rightarrow POF_3$$

being −71 kcal. per mole (*8*).

The observations on fluorophosphine complexes are consistent with the experience that halophosphines coordinate better than tertiary phosphines. The effect of the electronegativity of the fluorine atoms in phosphorus trifluoride or difluorophosphines in reducing the availability of the lone pair of electrons on the phosphorus alone would strongly limit the ability of the ligand to coordinate. On formation of the donor (sigma)-bond as the first step in coordination, a negative formal charge has to be assumed for the metal and a positive one for the ligand. This in turn leads to an increase of electron affinity of the unoccupied ligand $d\ \pi$-orbitals, and compensation of the formal charge with formation of a π-bond becomes possible. It is evident that both types of bonding mutually strengthen each other, giving rise to unexpectedly stable compounds of transition metals in unusual oxidation states, if the necessary $3d\pi$ orbital on the ligand is available.

The chemical and thermal stability of the fluorophosphine complexes is markedly increased in every case over the chlorophosphine complexes, none of the latter being volatile. The stability of the fluorophophine complexes as compared with the parent carbonyl is also noteworthy. While nickel carbonyl is distillable only with considerable decomposition, tetrakis(trifluorophosphine)nickel-(0) is far more stable on distillation at atmospheric pressure, and can also conveniently be handled in a high-vacuum system.

Tetrakis(trifluorophosphine)nickel-(0) is particularly illustrative, in that it could not be obtained by the direct reaction of phosphorus trifluoride with nickel carbonyl (*6*), because of lack of donating power of phosphorus trifluoride. Once formed by an indirect approach, however, the compound exhibits considerable stability and it is reasonable to attribute this effect to the back-donation of electrons from the metal to the ligand. It is in line with these observations that nitrogen trifluoride, although formally analogous to phosphorus trifluoride, does not act similarly as a ligand, because of its lack of $d\pi$ orbitals (*31*). The influence of the electronegative substituents on the phosphorus is demonstrated in the following series, where the tendency to form an adduct decreases as follows:

$F_3B.PR_3$	>	$F_3B.PCl_3$	>	$F_3B.PF_3$
Forms immediately		Dec. 6°		No combination
(*6*)		(*3*)		(*4, 6*)

It is peculiar that on the basis of a recent Raman spectroscopic investigation (*33*), the Ni-P stretching force constant in tetrakis(trifluorophosphine)nickel-(0)

is far lower than expected for a double bond. It is believed, therefore, that the type of dative bond, as outlined above, appears spectroscopically equivalent essentially to a single bond.

Experimental

The preparation of tetrakis(trifluorophosphine)nickel-(0), tetrakis(methyldifluorophosphine)nickel-(0), and tetrakis(phenyldifluorophosphine)nickel-(0) from the corresponding chloro compounds, using potassium fluorosulfinate as a fluorinating agent, has been described (*23*).

Tetrakis(phenyldifluorophosphine)nickel-(0). FLUORINATION WITH ARSENIC TRIFLUORIDE. The reaction was conducted in a 200-ml. two-necked flask, fitted with a stopcock adapter on one neck, and a reflux condenser with a drying tube and stopcock adapter on top. The system was evacuated, filled with nitrogen, and charged in a countercurrent of nitrogen with the solution of 23.3 grams (0.03 mole) of tetrakis(phenyldichlorophosphine)nickel-(0) (*17*) in 80 ml. of absolute benzene, and 21.1 grams (ca. 0.16 mole) of arsenic trifluoride. One gram of antimony pentachloride was added, and the brown mixture was refluxed with magnetic stirring for 3 hours. Contact with the atmosphere was prevented by passing nitrogen through a T-tube, attached to the adapter on top of the reflux condenser. After 10 hours' stirring at room temperature, the volatile products were removed in vacuo (1 mm.) at room temperature, and the solid residue was dissolved in benzene and filtered in a nitrogen atmosphere. The benzene was then evaporated in vacuo, the residue was dissolved in 100 ml. of ether, and charcoal was added to decolorize the product. The ether solution was partially evaporated and an equal volume of petroleum ether (b.p. 30° to 60°) was added. Upon cooling with ice the fluorophosphine complex crystallized [yield 10.5 grams (54%)]. The slightly brownish material was twice recrystallized from the minimum volume ether–petroleum ether (1:1). The colorless crystals thus obtained were dried in vacuo (m.p. 66–67°; previously reported m.p. 63.5°) (*23*).

Analysis. Calcd. for $C_{24}H_{20}F_8NiP_4$. C, 44.8; H, 3.2; F, 23.6; Ni, 9.1; P, 19.3. Found: C, 45.3; H, 3.4; F, 21.8; Ni, 9.1; P, 19.1. Mol. wt. (cryoscopic in benzene). Calcd., 643. Found, 597, 609.

Determination of the magnetic susceptibility showed the expected diamagnetism with $\chi_M = -88.1 \times 10^{-6}$ [cgs]) at 25° C.

INFRARED SPECTRUM OF TETRAKIS(PHENYLDIFLUOROPHOSPHINE)NICKEL-(0) (in potassium bromide). 3075, 2960 (w): υ_{C-H}; 1598 (m) 1490 (w): $\upsilon_{C^{-}C}$; 1440(s): ν_{P5C-H}[9]; 1385 (w); 1310 (w); 1282 (m); 1112 (s); 1000 (m): $\nu_{P-C_5H_6}$; 830 (m); 827 (vs), 796 (vs), 790 (sh): ν_{P-F}; 747, 712,690 (vs): C-H wagging.

Tetrakis(phenyldichlorophosphine)nickel-(0) does not exhibit any significant absorption in the 1000- to 750-cm.$^{-1}$ region.

FLUORINATION WITH ZINC FLUORIDE. The apparatus employed was the same as for arsenic trifluoride. In a countercurrent of nitrogen, 23.3 grams (0.03 mole) of tetrakis(phenyldichlorophosphine)nickel-(0) in 120 ml. of absolute benzene and 24.8 grams (0.24 mole; 100% excess) of zinc fluoride were placed in the reaction flask. The suspension was refluxed for 4 hours with magnetic stirring, and subsequently filtered hot in a nitrogen atmosphere. The viscous red-black residue was washed with hot benzene, and the filtrate was evaporated to dryness by removal of the benzene in vacuo. Decolorization of the crude product was as described above. Upon crystallization from ether–petroleum ether (1:1), a total of 7.3 grams (37.6%) of the flurophosphine complex (m.p. 65–66°) was obtained.

Analysis. Calcd. for $C_{24}H_{20}F_8NiP_4$. C, 44.8; H, 3.2. Found: C, 44.9; H, 3.5.

Reaction of Phenylphosphine with Nickel Carbonyl. A 50-ml. three-necked flask was equipped with a thermometer, a stopcock adapter, a magnetic stirrer, and a reflux condenser with a stopcock adapter on top, the latter being connected to a mercury valve. Then 13.2 grams (0.12 mole) of phenylphosphine (*14*) was distilled into the flask in vacuo, while the stopcock adapter was temporarily removed. The evacuated flask was filled with nitrogen, the phosphine was cooled to 0°, and 5.1 grams (0.03 mole) of nickel carbonyl was added by means of a hypodermic syringe in a countercurrent of nitrogen. Carbon monoxide was evolved briskly at room temperature, and stirring was continued for 5 hours. The evolution of carbon monoxide had subsided after another hour of stirring at 40° inner temperature. A colorless precipitate was formed upon cooling to −80°, but liquefied again at room temperature. One and one half grams of phenylphosphine was pumped off in vacuo, and the residue solidified immediately upon cooling with ice.

Attempts to purify the material further met with little success because of its extreme sensitivity toward oxygen. Recrystallization from ether, for instance, in a modified Schlenk tube (*25*), with exclusion of air, invariably led to an off-colored product. An attempt to sublime the product in a high vacuum resulted in complete decomposition. Analysis even on the crude product, however, confirmed its identity as a disubstituted derivative of nickel carbonyl.

Analysis. Calcd. for $C_{14}H_{14}NiO_2P_2$. C, 50.2; H, 4.2; Ni, 17.5; P, 18.5. Found: C, 48.7; H, 4.4; Ni, 16.8; P, 18.1. At. ratio Ni:P = 1:2.04.

INFRARED SPECTRUM (SOLID IN KBR). 3050 (w); 2310 (m):ν_{P-H}; 2010 (vs), 1945 (vs): ν_{C-O}, 1475 (m); 1430 (m); 1085 (m); 1025 (w); 916 (w); 880 (sh); 860 (vs, bd); 730 (vs); 692 (vs).

The product did not show a sharp melting point but decomposed rapidly above 60°. It is important to maintain the reaction temperature below 50°.

Chloromethyldifluorophosphine. A 50-ml. three-necked flask, I, was equipped with a solid addition funnel, a thermometer reaching to the bottom of the flask, and a magnetic stirrer. Flask I was attached to a downward condenser, which was connected to a 35-ml. two-necked flask, II, the latter being attached to an 8-inch helix-packed distillation column, fitted with a cow-type receiver. The system was evacuated and filled with nitrogen. In a countercurrent of nitrogen, 45.4 grams (0.3 mole) of chloromethyldichlorophosphine (*30*) was placed in flask I, while 54 grams (0.3 mole) of antimony trifluoride was charged into the solid addition funnel.

A slightly exothermic reaction took place when the antimony trifluoride was gradually added to the chlorophosphine. The temperature in flask I was maintained sufficiently high to allow distillation of the volatile fluorination products immediately after their formation. Material boiling at 35° to 55° was carefully redistilled at a slow rate. Chloromethyldifluorophosphine was collected, boiling at 33.5°–34.5°. Yield was 29.7 grams (83.5%).

Analysis. Calcd. for CH_2ClF_2P. F, 32.1; P, 26.2. Found: F, 32.3; P, 26.1.

A total of 0.8 gram of elemental antimony was isolated from the distillation residue in flask I, indicating that only a minor redox reaction had occurred.

Chloromethyldifluorophosphine ignites immediately in the atmosphere and consequently should be handled under nitrogen or in a vacuum line throughout. A sample of the fluorophosphine stored at approximately 0° for several weeks contained a sizable amount of chloromethyltetrafluorophosphorane, $ClCH_2PF_4$ (*22*), together with a solid material, as indicated by the F^{19} NMR spectrum of the former.

No satisfactory infrared spectrum of chloromethyldifluorophosphine in the gas phase could be obtained, since the sodium chloride windows of the gas cell were rapidly coated with a white substance. The P-F stretching frequency probably occurs between 900 and 830 cm.$^{-1}$, where a broad, very strong absorption was noted, while the C-Cl stretching frequency was found in the usual region at 710 cm.$^{-1}$.

Tris(chloromethyldifluorophosphine)molybdenum Tricarbonyl. A 25-ml. three-necked flask, I, fitted with a dry ice condenser with a drying tube, and a thermometer, was attached to a downward condenser, the latter being placed on a flask, II, containing 15.0 grams (0.125 mole) of chloromethyldifluorophosphine. The fluorophosphine was cooled with liquid nitrogen and the system was carefully evacuated and filled with nitrogen. A nitrogen atmosphere was maintained throughout the experiment by running a slow stream of the gas through a T-tube on top of the dry ice reflux condenser. In advance 2.72 grams (0.01 mole) of cycloheptatriene molybdenum tricarbonyl (*1*) had been placed in flask I and was cooled to −80° while the fluorophosphine was distilled over. An exothermic reaction was noted when the temperature was allowed to rise gradually to room temperature, and occasional cooling with ice became necessary. The dark brown reaction mixture was stirred for 25 minutes at an inner temperature of 30° to 40°. The products, which are volatile at room temperature (essentially excess fluorophosphine) were then removed in vacuo (1 mm.) and condensed in a cool trap for disposal. The remaining residue was extracted with three 25-ml. portions of hexane. The combined extracts were filtered in the atmosphere, and the volatile solvent was stripped off in vacuo to leave 3.9 grams (73%) of the crude complex, which was subsequently distilled under high vacuum. Tris(chloromethyldifluorophosphine)molybdenum tricarbonyl was collected at 127° at 0.05 mm.; 2.75 grams of an almost colorless, air-stable liquid was obtained (n_D^{25} = 1.5797). The refractive index was found unchanged after 3 months' storage.

Analysis. Calcd. for $C_6H_6Cl_3F_6MoO_3P_3$. C, 13.5; H, 1.1; F, 21.3; Mo, 17.9. Found: C, 14.4; H, 1.5; F, 21.3; Mo, 18.3.

INFRARED SPECTRUM (LIQUID IN BENZENE). 2985 (w), 2932 (m): C-H; 2038 (vs), 1970 (vs): Co; 1391 (s); 1205 (w); 1134 (s), 1110 (s); 866, 842, 821 (vs, bd): P-F; 780 (s); 700 (s): C-Cl.

CO Stretching Frequencies in Molybdedum Tricarbonyl Derivatives

$(PF_3)_3Mo(CO)_3$[a]	2085 (vs), 2055 (vs), 1990 (vs)[b,c]
$(PCl_3)_3Mo(CO)_3$	2040 (vs), 1990 (vs)[b,c]
$(ClCH_2PF_2)_3Mo(CO)_3$	2038 (vs), 1970 (vs)[d]
$C_7H_8Mo(CO)_3$	1972 (vs), 1905 (vs), 1856 (vs)[b,c]

[a] Not yet obtained in satisfactory purity prepared by metathetical reaction from $(PCl_3)_3$-$Mo(CO)_3$ (*2*) with potassium fluorosulfinate. In addition to carbonyl absorptions, infrared spectrum exhibits only strong P—F stretching absorptions at 852 cm.$^{-1}$ (m), 867 cm.$^{-1}$ (vs), and 880 cm.$^{-1}$ (sh), in the region for phosphorus trifluoride (*10*).

[b] Solid in KBr.

[c] Infrared data taken on KBr pellets may be somewhat uncertain, and recently, infrared data of metal carbonyl derivatives obtained on solids were rejected because of possible crystal splitting of bands (*19*).

[d] Liquid in benzene.

Acknowledgment

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Literature Cited

(1) Abel, E. W., Bennett, M. A., Burton, R., Wilkinson, G., *J. Chem. Soc.* **1958**, 4559.
(2) Abel, E. W., Bennett, M. A., Wilkinson, G., *Ibid.*, **1959**, 2323.
(3) Baumgarten, P., Bruns, H., *Ber.* **80**, 517 (1947).
(4) Booth, H. S., Walkup, J. H., *J. Am. Chem. Soc.* **65**, 2334 (1943).
(5) Chatt, J., *Nature* **165**, 637 (1950).
(6) Chatt, J., Williams, A. A., *J. Chem. Soc.* **1951**, 3061.
(7) Dawson, T. P., Kennard, K. C., *J. Org. Chem.* **22**, 1671 (1957).
(8) Ebel, F., Bretscher, E., *Helv. Chim. Acta* **12**, 450 (1929).
(9) Grieb, C. M. W., Jones, R. H., *J. Chem. Soc.* **1932**, 2543.

(10) Gutowsky, H. S., Liehr, A. D., *J. Chem. Phys.* **20**, 1652 (1952).
(11) Irvine, J. W., Wilkinson, G., *Science* **113**, 742 (1951).
(12) Kodama, G., Parry, R. W., *J. Inorg. Nucl. Chem.* **17**, 125 (1961).
(13) Kosolapoff, G. M., "Organophosphorus Compounds," pp. 241 ff., Wiley, New York and London, 1958.
(14) Kuchen, W., Buchwald, H., *Ber.* **91**, 2296 (1958).
(15) Kulakova, V. N., Zinov'ev, Yu. M., Soborovskii, L. Z., *J. Gen. Chem. USSR* **29**, 3916 (1959) (Engl. transl.)
(16) Maier, L., *Angew. Chem.* **71**, 574 (1959).
(17) Malatesta, L., Sacco, A., *Ann. chim.* (*Rome*) **44**, 134 (1954).
(18) Orgel, L. E., "Introduction to Transition Metal Chemistry," p. 143, Wiley, London and New York, 1961.
(19) Orgel, L. E., *Inorg. Chem.* **1**, 25 (1962).
(20) Quin, L. D., *J. Am. Chem. Soc.* **79**, 3681 (1957).
(21) Schmutzler, R., *J. Inorg. Nucl. Chem.*, in press.
(22) Schmutzler, R., *Chem. and Ind.* (*London*) **1962**, 1868.
(23) Seel, F., Ballreich, K., Schmutzler, R., *Ber.* **94**, 1173 (1961).
(24) *Ibid.*, **95**, 199 (1962).
(25) Seel, F., Hadji-Walassis, N., *Z. anorg. allgem. Chem.* **261**, 85 (1950).
(26) Seel, F., Jonas, H., Riehl, L., Langer, J., *Angew. Chem.* **67**; 32 (1955).
(27) Seel, F., Riehl, L., *Z. anorg. allgem. Chem.* **282**, 293 (1955).
(28) Seel, F., Langer, J., *Angew. Chem.* **68**, 461 (1956).
(29) Seel, F., Langer, J., *Z. anorg. allgem. Chem.* **295**, 316 (1958).
(30) Uhing, E., Rattenbury, K., Toy, A. D. F., *J. Am. Chem. Soc.* **83**, 2299 (1961).
(31) Wilkinson, G., *Nature* **168**, 514 (1951).
(32) Wilkinson, G., *J. Am. Chem. Soc.* **73**, 5501 (1951).
(33) Woodward, L. A., Hall, J. R., *Spectrochim. Acta* **16**, 654 (1960).
(34) Yagupol'skii, L. M., Ivanova, Zh. M., *J. Gen. Chem. USSR* **29**, 3726 (1959) (Engl. transl.).

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Metal Chelate Compounds as Acid Catalysts in Solvolysis Reactions

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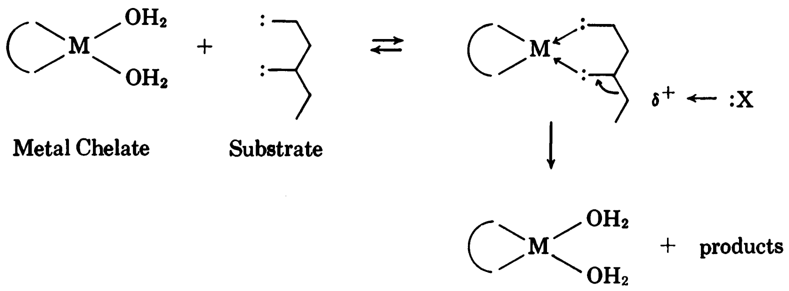
Examples of metal chelate catalysis are given in which the metal ion acts as a Lewis acid in the activation of the reaction between a substrate and a nucleophilic reagent. Requirements for maximum activity of Cu(II) chelates in the catalysis of the solvation of diisopropylphosphorofluoridate (DFP), and isopropylmethylphosphonofluoridate (Sarin) are maximum positive charge on the complex, minimum number of coordination sites of the metal ion occupied by the ligand, and minimum formation of μ-dihydroxo binuclear species. Catalysis of salicyl phosphate hydrolysis is described for the aquo Cu(II), bipyridine-Cu(II) ion, *N*-hydroxyethylethylenediamine-Cu(II), and VO(IV) ions, and the 1:1 and 2:1 vanadyl chelates of 3,5-disulfopyrocatechol. A general mechanism proposed for metal ion and metal chelate-catalyzed hydrolysis is a combination of the substrate with the metal ion in such a manner that intramolecular nucleophilic attack of the phosphate group by the carboxylate group is note prevented. The inactivity of the mixed salicyl phosphate bipyridine-CU(II) complex and the activity of the corresponding 1,3-dicarboxyphenyl-2-phosphate complex are in accord with this mechanism.

This investigation of the catalysis of solvolysis reactions by metal chelate compounds is an outgrowth of our previous studies of solution equilibria and stabilities of metal chelates. Of particular interest as catalysts are the chelates in which the ligand does not completely satisfy the coordination requirements of the metal ion. Compounds of this type undergo interesting reactions such as hydrolysis (hydroxo complex formation), and olation (bridging of metal ions by hydroxyl ions), to give polynuclear complexes. The residual coordinating tendencies of the metal ion in these metal chelate compounds, which are responsible for their hydrolysis and olation reactions, also impart catalytic activity to these complexes.

The catalytic effect is achieved through the weak Lewis acid properties of the metal ion as the "active site" in the metal chelate compound. The residual Lewis acid activity of aquo metal ions and "incompletely coordinated" metal ions in complexes and chelates in aqueous solution is actually very weak compared to that of the hydrogen ion; on the other hand, metal ions and complexes are available in solution at high pH values, where the concentration of hydrogen ions is so low that their catalytic effect cannot be significant.

Of particular interest as catalysts are the incompletely coordinated metal chelate compounds, which are sufficiently stabilized by the ligand to be stable in solution at pH values much higher than that at which the aquo metal ion would precipitate as the hydroxide and thus to become unavailable for homogeneous catalysis. Such a metal chelate would be particularly effective as a catalyst for the activation of a substrate which can coordinate to the metal ion in the chelate compound. The interaction of the substrate with the metal ion would increase its reactivity toward nucleophilic reagents such as solvent molecules or hydroxyl ions in accordance with the following scheme:



It is apparent that coordination of the substrate with the metal ion would increase its reactivity toward hydroxyl ions and other nucleophilic reagents.

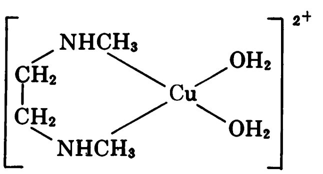
Because the electronic interaction of the metal ion with the substrate is considerably lower than that of the hydrogen ion, it is proposed that the metal ion be considered a "subproton" in these catalytic reactions. Thus, the catalytic effect expected of the hydrogen ions, if available at the same concentration (and conditions) as the metal ion or metal chelate, would be expected to be much greater. Although the metal chelate is an extremely weak Lewis acid, it has some special properties not possessed by the proton. By virtue of its coordination number, size, and the steric requirements of its coordinate bonds, it would be expected to have a high degree of specificity, with respect to both the nature of the substrate with which it combines and the selectivity of interaction with specific groups within the ligand. The considerable specificity that is theoretically possible in metal chelate catalysis makes this type of study of considerable interest for the study of reaction mechanisms.

Metal Chelate Catalysis in Solvolysis of Fluorophosphates

The solvolysis of fluorophosphates such as methylisopropylphosphonofluoridate (Sarin) and diisopropylphosphorofluoridate (DFP) has been found to be catalyzed by a number of metal ions and metal chelates such as I to VI (5). The catalytic solvolysis reactions are generally first order in metal chelate concentration, in substrate concentration, and in hydroxyl ion. As is suggested by these examples, the catalytic activity decreases as the negative charge of the ligand increases, and as the number of coordination positions on the metal ion which are satisfied by the ligand increase. For a completely coordinated and stable metal chelate, such as Cu(II)-trien(VI), there is very little activity. The aquo metal ion is generally the most effective catalyst, but its pH range of solubility is so low that very little free Cu^{+2} ion is in solution in the pH range (7 or higher) where the hydroxyl ion is available in sufficient concentrations to give a reasonably high rate of hydrolysis. For metal chelates and complexes of Cu(II), it is necessary to have at least a bidentate donor coordinated to the metal ion to achieve reasonable stability in dilute solution, so that the most effective Cu(II) complexes are those having a 1 to 1 molar ratio of a bidentate neutral ligand to the metal ion.

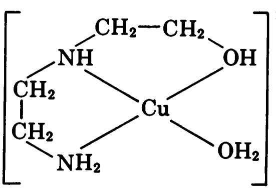
Half-Times of First-Order Sarin Hydrolysis

(t = 25°; -log $[H^+]$ = 7.0; [Sarin] = [metal chelate] = 10^{-3} M)



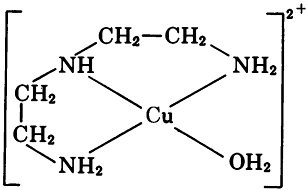
I

N,N'-Dimethylethylenediamine-Cu(II) ion; $t_{1/2}$ = 3.5 min.



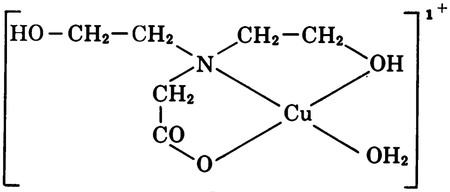
II

N-Hydroxyethylethylenediamine-Cu(II) ion; $t_{1/2}$ = 15 min.



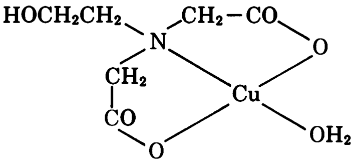
III

Diethylenetriamine-Cu(II) ion; $t_{1/2}$ = 25 min.



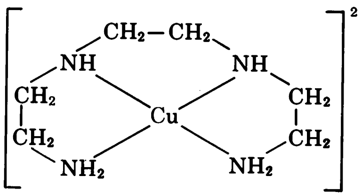
IV

N, N-Dihydroxyethylglycino-Cu(II) ion; $t_{1/2}$ = 25 min.



V

N-Hydroxyethyliminodiacetato-Cu(II) ion; $t_{1/2}$ = 57 min.



VI

Triethylenetetramine-Cu(II) ion; $t_{1/2}$ = 65 min.

Experimental measurement (6, 8) of the solvolysis of Sarin and DFP in the presence of 1 to 1 diamine-metal chelates, such as those listed in Table I, under varying solution conditions showed that the catalytic effect was not proportional to, or a simple function of, the total metal chelate species in solution. A detailed analysis of the variation of rate with composition of the solutions indicated (4, 7) the presence of hydroxo and dihydroxo mononuclear forms of the chelate compound, as well as a binuclear μ-dihydroxo species. If the possible reactivities of all catalytic species are taken into consideration, the rate expression would have the form:

$$k_{obsd} = k_{CuL}[CuL^{+2}][OH^-] + k_{Cu(OH)L}[Cu(OH)L^{+1}] + k_{Cu_2(OH)_2L_2}[Cu_2(OH)_2L_2^{+2}] \cdot + k_{Cu_2(OH)_2L}[Cu(OH)_2L] + k_{Cu}[Cu^{+2}][OH^-] + k_{H_2O}$$

Near the neutral region (pH 6 to 8) the concentration of the base, $Cu(OH)_2L$, is negligible. The constants k_{Cu} and k_{H_2O} can be determined independently, while the influence of concentration on k_{obsd} can be employed to show $k_{Cu_2(OH)_2L_2}$, the catalytic effect of the binuclear form, to be negligibly small. Thus it is possible to determine $k_{CuL} + k_{Cu(OH)L}$, which are seen to be indistinguishable, since they are related to each other by the hydrolysis constant of the normal chelate compound—i.e., $k_{CuL}K_B[CuL^{+2}][OH^-] = k_{Cu(OH)L}[Cu(OH)L^+]$, where $K_B = [Cu(OH)L^+]/[CuL^{+2}][OH^-]$).

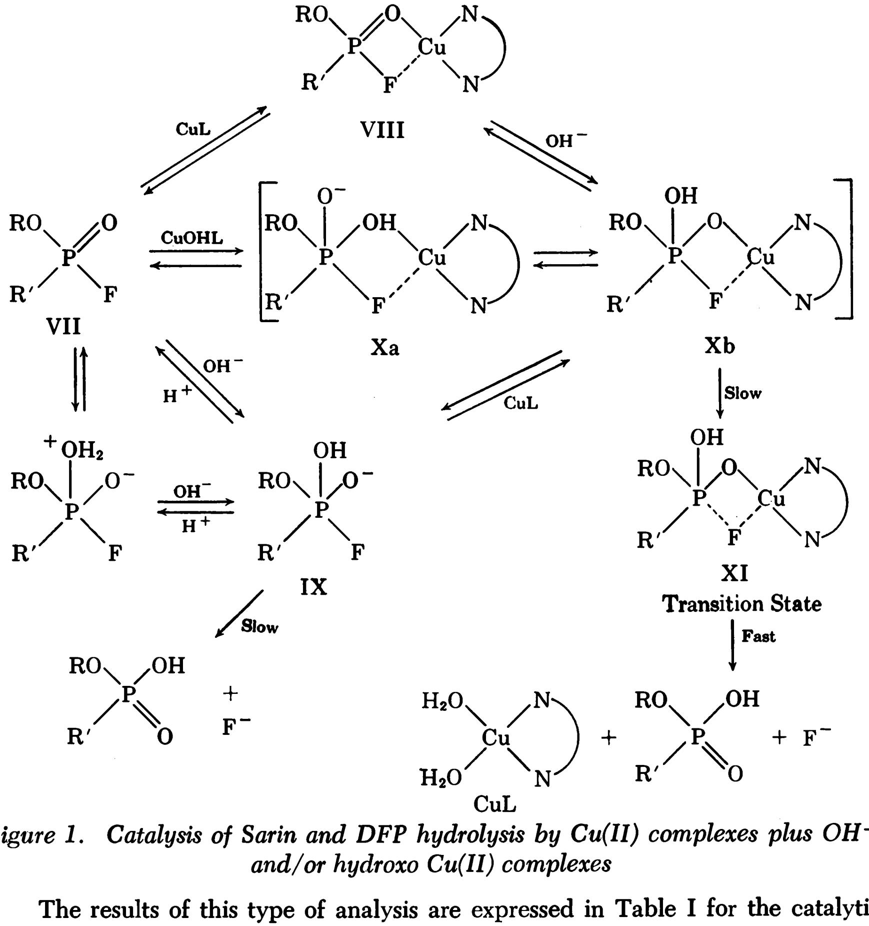


Figure 1. Catalysis of Sarin and DFP hydrolysis by Cu(II) complexes plus OH⁻ and/or hydroxo Cu(II) complexes

The results of this type of analysis are expressed in Table I for the catalytic effects of Cu(II) chelates on the hydrolysis of Sarin (*8*) and DFP (*6, 8*).

Although there has been considerable disagreement in the literature as to whether the catalytically active species is CuL^{+2} or $Cu(OH)L^+$, it is seen from the mechanism outlined in Figure 1 that such distinctions are meaningless. Since the rate-determining step is probably the breaking of the phosphorus-fluorine bond (XI), the substrate (VII), metal chelate (CuL), and hydroxyl ion are involved in a number of interdependent pre-equilibria, all leading to the same monoprotonated reactive intermediate, which exists in two (or more) tautomeric forms, Xa and Xb. More basic catalysts indicated in the general rate law lead to a less protonated intermediate, or react by direct attack on the phosphorus atom.

The constants listed in Table I reflect the significance of the hydrolysis and

Table I[a]. Third-Order Rate Constants Assigned to 1:1 Cu(II) Chelates as Catalysts in the Hydrolysis of Sarin and DFP at 25°

Ligand	*DFP*[b]	*Sarin*[b]
TMEN, H_2O	7.0×10^6	1.0×10^8
DMEN, H_2O	2.3×10^6	3.2×10^7
DIPY, H_2O	7.4×10^6	3.1×10^7
PHEN, H_2O	4.9×10^6	1.9×10^7
HEN, H_2O	6.4×10^5	9.3×10^6
DHEN, H_2O	4.0×10^5	5.2×10^6

[a] Metal chelates contain 1:1 molar ratio of ligand to metal ion. TMEN = tetramethylethylenediamine; DMEN = dimethylethylenediamine; DIPY = α,α′-bipyridine; PHEN = *o*-phenanthroline; HEN = *N*-hydroxyethylethylenediamine; DHEN = *N,N′*-dihydroxyethylethylenediamine.

[b] Units are $l.^2$ $mole^{-2}$ $sec.^{-1}$; rates proportional to concentrations of substrate, OH^-, and metal chelate compound.

dimerization tendencies of the metal chelates. The more highly coordinated forms, such as the Cu(II) chelates of HEN and DHEN, are actually less active, as expected, than the chelates of the strictly bidentate ligands such as bipyridine or *N,N′*-dimethylethylenediamine. However, the level of catalytic activity achieved experimentally does not follow the rate constants listed in Table I, because of the differences in the tendencies of these metal chelates to form inactive binuclear complexes. This is especially noticeable for the bipyridine and tetramethylethyllenediamine complexes, which do not differ significantly in catalytic activity with respect to the hydrolysis of DFP. However, the latter is many times more effective as a catalyst experimentally, since the bipyridine-Cu(II) complex is almost completely converted to the inactive binuclear species, while the tetramethylethylenediamine-Cu(II) chelate has much less tendency to dimerize.

The minor variations in the rate constants of analogous chelate compounds listed in Table I are probably due to steric effects which influence the coordination of the copper(II) ion to the substrate, and to differences in the electronic interactions between metal ion and substrate, which arise from the differences in stability of the coordinate bonds in the metal chelate compounds.

Salicyl Phosphate

Metal ion catalysis of salicyl phosphate hydrolysis is much more complicated than that of Sarin, since the former substrate can combine with metal ions to give stable complexes, and some of the complexes formed do not constitute pathways for the reaction. In addition the substrate undergoes intramolecular acid-base–catalyzed hydrolysis which is dependent on pH because of its conversion to a succession of ionic species having different reaction rates. Therefore a careful and detailed equilibrium study of proton and metal ion interactions of salicyl phosphate would be required before any mechanistic considerations of the kinetic behavior in the absence and presence of metal ions can be undertaken.

Catalysis by Cu(II) Ion and Cu(II) Complexes. The rate profiles for the hydrolysis of salicyl phosphate in the absence of metal ions, and in the presence of an equimolar concentration of Cu(II) ion, are given in Figure 2. As the pH increases, the rate of hydrolysis of salicyl phosphate increases because of conversion of the carboxyl group to the carboxylate anion. The latter is required for the reaction, which is considered to take place via intramolecular nucleophilic attack of the carboxylate group in the phosphorus atom, as first suggested by Chanley and coworkers (*1, 2, 3*). As the pH is further increased, the rate of reaction begins to drop off as the result of the dissociation of the proton attached to the phosphate group. The fully dissociated substrate hydrolyzes only very slowly, since the negative phosphate group repels the negative carboxylate group—i.e., it loses its electrophilic properties. Thus an acid catalyst (the proton) and a basic group (the carboxylate group) must both be present in the substrate to give the rate behavior described above. The intramolecular acid-base–catalyzed reaction mechanism was recently further elaborated (9) to include acid catalysis by metal ions and metal complexes, according to the scheme shown in Figure 3.

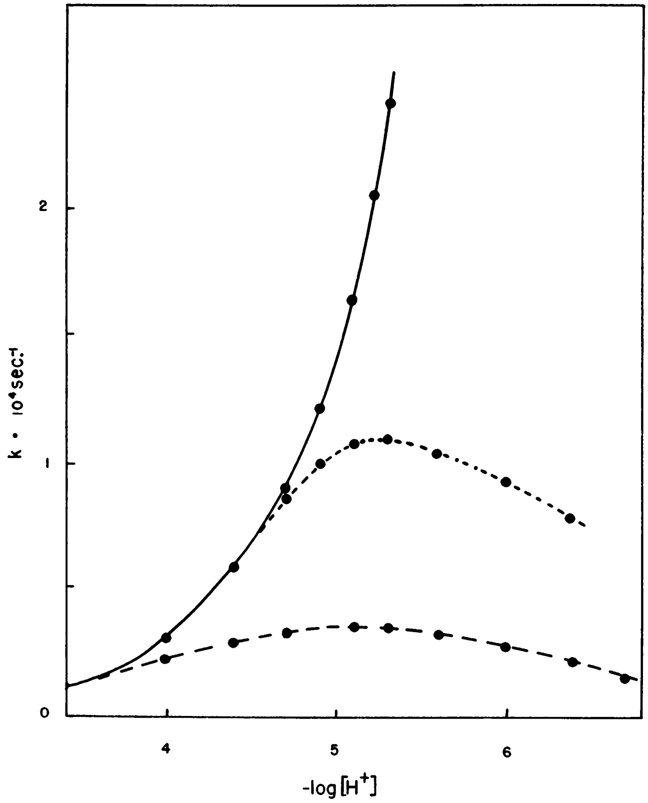


Figure 2. Rate profiles for hydrolysis of 1.00 x $10^{-3}M$ salicyl phosphate at 30°

$\mu = 0.10$ (KNO_3)
——In presence of 1.00 × $10^{-3}M$ Cu(II) salt
. . . . In presence of 1.00 × $10^{-3}M$ N-hydroxyethylethylenediamine – Cu(II) chelate

The assignment of rate constants to two species of the substrate is interesting in view of the requirements of the reaction mechanism given above. Since the formation of the activated intermediate requires a free carboxylate species, the monoionic form of the substrate must react through a rearrangement of the proton from the carboxyl to the phosphate group (XIIIa ⇌ XIIIb). If the dissociation constants of the diprotonated phosphate and carboxyl groups are considered to differ by a factor of about 100, the intrinsic rate constant of XIIIb would be estimated as about 5 × 10^{-4} sec. $^{-1}$ at 30°. This is considerably greater than the value of 4 × 10^{-5} sec.$^{-1}$ assigned to XIV, as it should be, in view of the

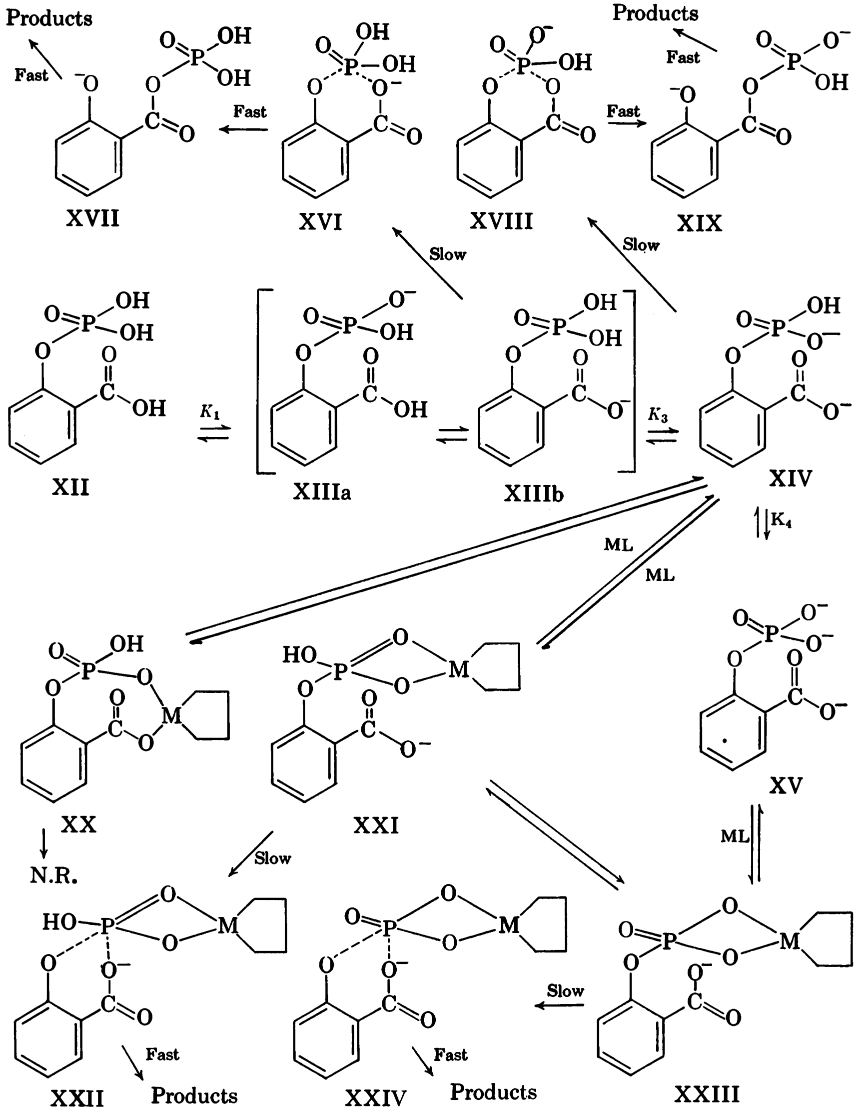


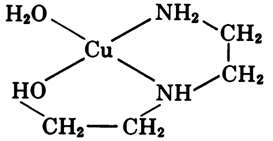
Figure 3. Mechanism of salicyl phosphate hydrolysis in presence and absence of metal complexes

greater electrophilic character imparted to the phosphorus atom by the two protons attached to the phosphate group.

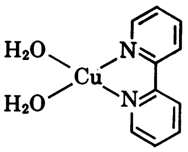
In the presence of an equimolar amount of Cu(II) salt, the rate profile shows a steadily increasing reaction velocity as the pH increases, until a practical limit is attained, as a result of the precipitation of copper hydroxide. There is no indication that the rate might level off or decrease at higher pH, as is true for the metal-free ligand. On this basis it seems that the metal ion combines with the substrate in such a way as to increase its reactivity toward the adjacent carboxylate group, as indicated in Figure 3 (formulas XXI and XXIII). Since increasing pH does not result in the dissociation of these reactive forms of the metal substrate chelate, the rate profile for metal ion catalysis should give maxima at higher pH than that of the metal-free reaction. The rate curve may or may not level off or decrease in value at much higher pH, depending on subsequent reactions of the active metal chelate complex. Possible reactions that would result in a decrease in the catalytic effect are disproportionation of the metal chelate and precipitation of the metal hydroxide, formation of hydroxo derivatives of XXIII, and formation of polynuclear complexes from the hydroxo form through olation reactions. It is seen from the mechanism in Figure 3 that the Cu(II) ions and complexes in XXI and XXIII take the place of one or more protons in imparting electrophilic reactivity to the phosphorus atom. The extent to which such catalytic activity occurs depends on the interaction between the metal ion and the phosphate groups of the ligand—i.e., the stabilities of metal chelate compounds XXI and XXIII.

The metal ion catalysis is complicated by the fact that the metal ion can combine with the substrate in more than one way. If the metal ion combines simultaneously with the carboxylate and phosphate groups, as indicated by XX, it is apparent that the resulting structure would not be a pathway for the reaction. Thus one would expect the metal substrate system to consist of a mixture of active and inactive forms, with the ratio between them variable and dependent on both the nature of the metal ion and the pH of the solution.

To determine the nature of the catalysis of salicyl phosphate hydrolysis by metal chelates, two diamine-Cu(II) chelates were selected for detailed study, *N*-*β*-hydroxyethylethylenediamine-Cu(II) ion (XXV) and *α*,*α*′-bipyridine-Cu(II) ion (XXVI) (*11*).



XXV



XXVI

To assign rate constants to specific solution species, the equilibria in the ternary system Cu(II)–salicyl phosphate–bipyridine were studied in detail by potentiometric pH measurements. The results, indicated in Figure 4, show

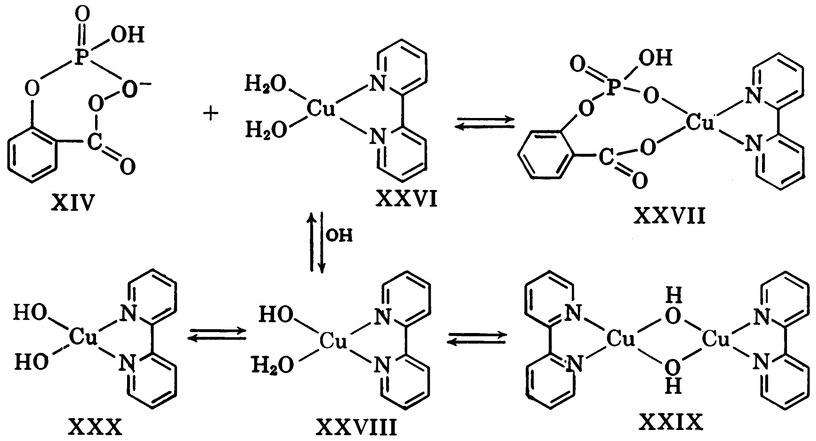


Figure 4. Cu(II)-bipyridine–salicyl phosphate equilibria

that a 1:1 bipyridine-Cu(II) chelate (XXVI) is formed at low pH, and that it undergoes hydrolysis and dimerization reactions as described previously by Gustafson and Martell (*7*). At high pH, however, the bipyridine complexes are converted to a mixed chelate, which is believed to have the structure indicated by XXVII. Experimentally, it was found that the rate of solvolysis of salicyl phosphate in the presence of bipyridine-Cu(II) is less than that of the substrate in the absence of metal ions. It was therefore concluded that the Cu(II)-bipyridine chelate itself, and its hydrolyzed forms, are relatively inactive, and that the mixed chelate (XXVII) is not a pathway for the reaction.

For catalysis by the Cu(II)–*N*-hydroxyethylethylenediamine chelate, it is seen from Figure 2 that the rate profile is similar to that of the pure ligand, except that the maximum is very much higher. The decrease of the catalytic effect at high pH values is a little surprising, however, in view of the above comments on the expected variation of metal ion catalysis in the higher pH region. If the metal chelate is a catalyst, one would expect the maximum to be displaced to much higher pH than that of the pure substrate. Potentiometric titration of the mixed complex system revealed no indication of the formation of a mixed complex, probably because the ligand which functions as a carrier of the metal ion is terdentate, thus reducing the coordination tendency of the metal ion for a second ligand. Analysis of the kinetic data failed to give a correlation between the observed rate and the concentrations of the metal chelate species present. On the other hand, the experimentally observed rate follows very closely the activity expected for the free metal ion calculated from the equilibrium constants (*7*) for the HEN-Cu(II) chelate system. Thus in this case the ligand acts as only a carrier for the metal ion, producing a buffer system which regulates the concentration of the free metal ion at a level sufficiently low that precipitation of the metal hydroxide does not take place. The fact that a homogeneous system is maintained in this way makes it possible to study catalysis by the free metal ion. The rate constants calculated from this analysis of the kinetic data gave the following rate constants for the Cu(II) chelates indicated in Figure 3:

$$k_{\mathrm{XX}} = 0;\; k_{\mathrm{XXI}} = 4.0 \times 10^{-2};\; k_{\mathrm{XXIII}} = 4\ (M^{-1}\,\mathrm{sec.}^{-1})$$

where M represents the Cu(II) ion not coordinated to HEN.

Thus it is seen that Cu(II) does not catalyze the hydrolysis of the mononegative ion, as probably would be expected because this form of the substrate would have little affinity for the metal ion. Maximum catalytic activity is realized in structure XXIII rather than XXI, because the former is in equilibrium with a smaller concentration of inactive forms analogous to XX and with a relatively higher concentration of the inactive tautomeric form of XXI.

Catalysis by VO(IV) Ion and VO(IV) Complexes. Catalysis of salicyl phosphate hydrolysis by the VO^{+2} ion and by the 1 to 1 vanadyl-3,5-disulfopyrocatechol (Tiron) system (*9*) is illustrated in Figure 5. It is seen that the catalytic effect of the VO(IV) ion is much higher than that of the Cu^{+2} ion. The interaction of the vanadium atom with the ligand would be expected to be somewhat greater than that of Cu^{+2}, because of the highly polar character of the vanadium-oxygen bond, which increases the effective charge on the vanadium atom to a value higher than that of the Cu^{+2} ion. At high pH the catalytic effect decreases, in accordance with the formation of relatively inactive hydroxo species. The equilibria outlined in Figure 6 have been reported for the equilibrium interactions between the vanadyl ion and salicyl phosphate (*10*).

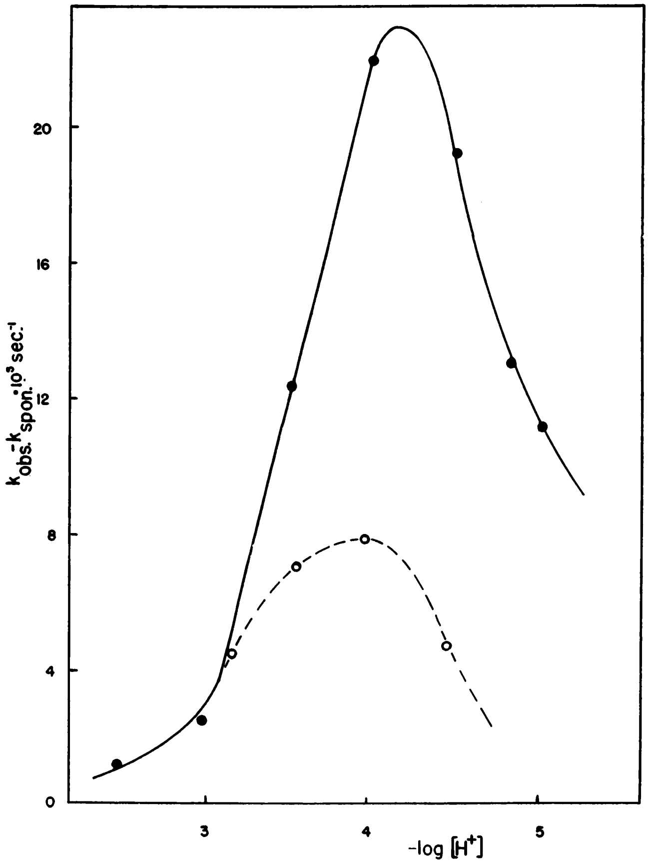


Figure 5. Rate profiles for catalytic hydrolysis of 1.00 x $10^{-3}M$ salicyl phosphate at 25°

$\mu = 0.10$ (KNO_3)
—In presence of equivalent concentration of vanadyl salt
- - - In presence of equivalent concentration of 2:1 Tiron-VO^{+2} chelate

The hydroxo and olated species indicated would be expected to have little or no activity, so that the observed rate would be expected to correlate with the concentration of the aquo vanadyl ion.

Correlation of the observed rates with the concentrations of the substrate species (*10*) indicates that the metal ion does not catalyze the hydrolysis of the monoanionic form of salicyl phosphate. Combination of the monoanionic form of the substrate with the vanadyl ion would result in an unreactive complex having a neutral carboxyl group. Shift of the proton to the phosphate group could not take place in accordance with the requirements of the general reaction mechanism illustrated in Figure 3. Thus the vanadyl ion would be expected to catalyze the hydrolysis of only the di- and trinegative forms of the substrate.

The rate profile for the catalytic effect of the system having a 2 to 1 molar ratio of Tiron to VO^{+2}, illustrated in Figure 5, shows that the activity of the metal chelate is much less than that of the metal ion. The catalytic effect of the 2 to 1 chelate system (which contains both the 1 to 1 and 2 to 1 chelates) is

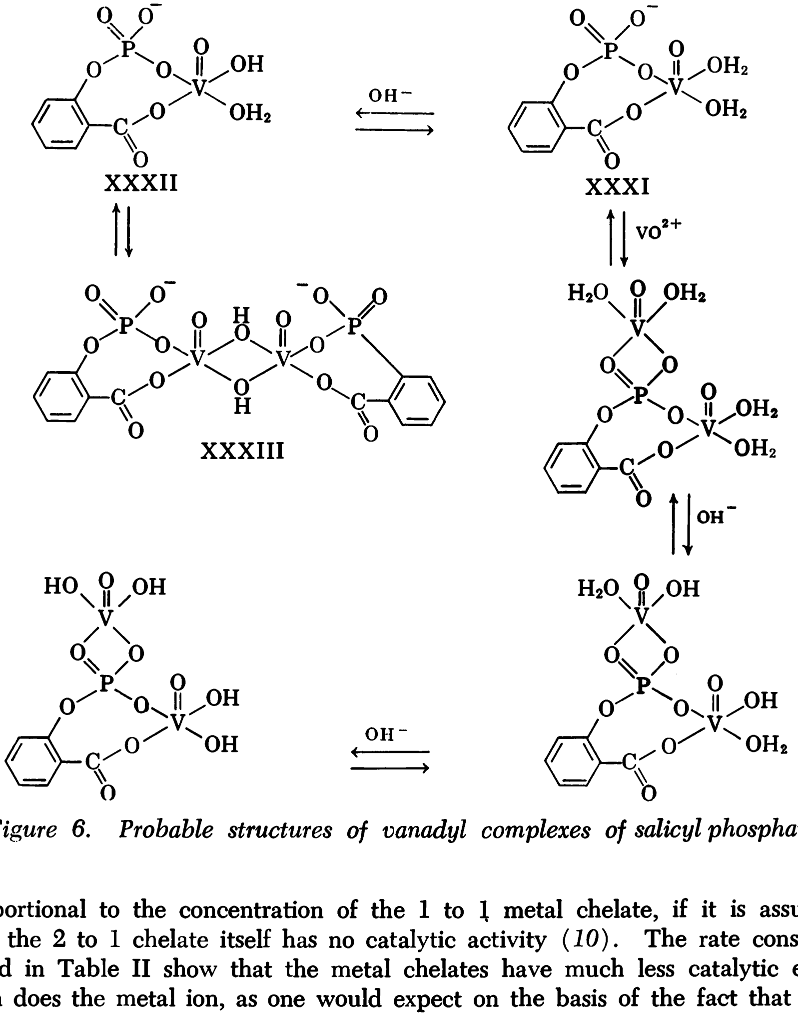


Figure 6. Probable structures of vanadyl complexes of salicyl phosphate

proportional to the concentration of the 1 to 1 metal chelate, if it is assumed that the 2 to 1 chelate itself has no catalytic activity (*10*). The rate constants listed in Table II show that the metal chelates have much less catalytic effect than does the metal ion, as one would expect on the basis of the fact that they are much weaker Lewis acids. The inactivity of the 2 to 1 Tiron–vanadyl chelate compound is attributed to the fact that the metal ion is well shielded by the two Tiron anions and cannot combine with the substrate.

Table II. Rate Constants for VO^{+2} and Vanadyl Chelate–Catalyzed Hydrolysis of Salicyl Phosphate

[25°, μ = 0.10 (KNO_3)]

Catalyst[a]	k (M^{-1} *Sec.*$^{-1}$)[b]
None	1.65×10^{-5} [c]
VO^{+2}	1.0×10^{-1}
VOSA[d]	7.5×10^{-2}
$VOTiron^{-2}$ [e]	4.3×10^{-2}
VOHQS[f]	3.8×10^{-2}
$VOSSA^{-}$ [g]	3.6×10^{-2}

[a] [Catalyst] = [substrate] = 1.00×10^{-3} *M*. [b] Second-order rate constants (reactions first-order in substrate and first-order in catalyst). [c] First-order, sec.$^{-1}$ (substrate only) [d] SA^{2-} = salicylate anion. [e] $Tiron^{-4}$ = 3,5-disulfopyrocatechol anion. [f] HQS^{-2} = 5-sulfo-8-quinolinol anion. [g] SSA^{-3} = 5-sulfo-8-hydroxyquinoline anion.

1,3-Dicarboxyphenyl-2-phosphate

The rate profile (*11*) for the hydrolysis of 1,3-dicarboxyphenyl-2-phosphate (DCPP) in the absence and presence of an equivalent amount of the bipyridine-Cu(II) chelate is shown in Figure 7. The catalytic effect of the metal chelate in this case is in marked contrast to the negative effect observed by the same chelate with salicyl phosphate. Analysis of the kinetic data as a function of the concentration of the metal chelate species indicates that the observed rate correlates well with the summation of the rates assigned to the individual tri- and tetranegative species of the substrate, in accordance with the mechanism on page 173.

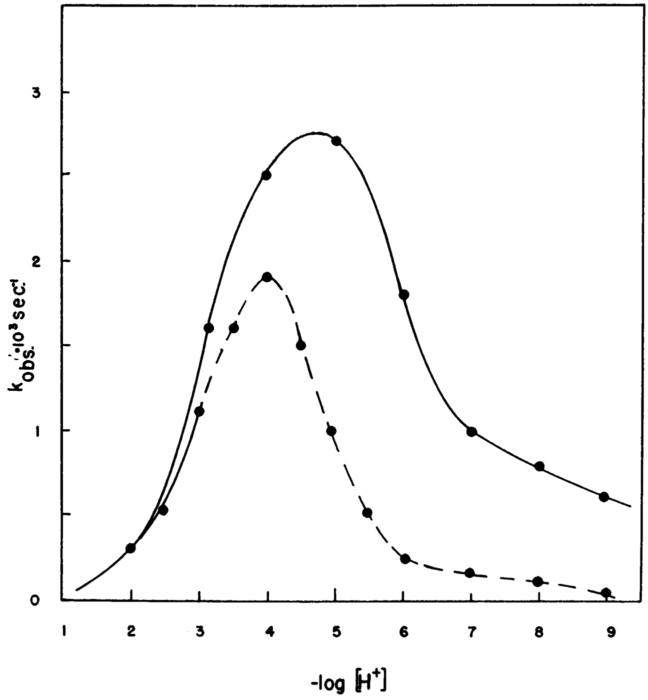
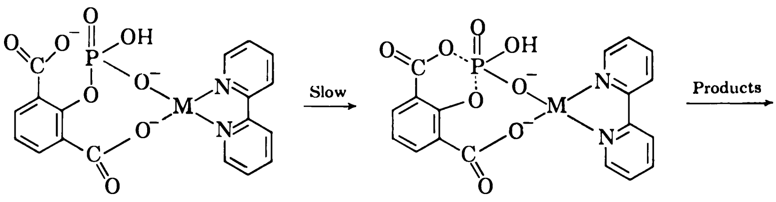


Figure 7. Rate profiles for hydrolysis of 1.00 × 10^{-3}M DCPP at 35°

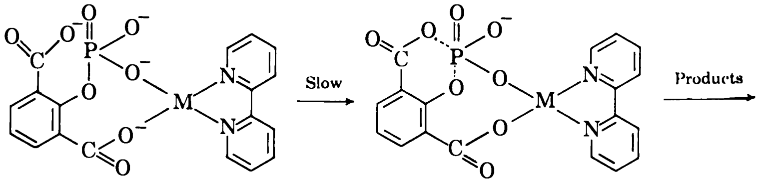
$\mu = 0.10$ (KNO_3)
—In presence of 1.00 × 10^{-3}M bipyridine-Cu(II) ion
- - - In absence of catalytic metal ions

In this system it was found that the catalytic effects of dihydroxo and binuclear μ-dihydroxobipyridine–Cu(II) chelates were negligible, but that neutral and monohydroxochelates were active catalysts.

Of special interest is the comparison of the inactivity of bipyridine-Cu(II) as a catalyst in salicyl phosphate hydrolysis, with its strong catalytic effect on the hydrolysis of dicarboxyphenyl-2-phosphate. A comparison of formulas XXVII with XXXIV and XXXVI shows that mixed complex formation of Cu^{+2} with salicyl phosphate and bipyridine would prevent attack of the phosphate group via the proposed mechanism. The formation of the analogous mixed chelate with DCPP (XXXIV and XXXVI) would produce a reaction intermediate for the reaction, since the metal ion would tie up one of the carboxylate ions but leave



XXXIV XXXV



XXXVI XXXVII

the other one free, while increasing the electrophilic activity of the phosphate group through complex formation with a phosphate oxygen atom. These observations are therefore in accord with the general mechanism for metal ion and metal chelate catalysis of salicyl phosphate hydrolysis illustrated in Figure 3.

Literature Cited

(1) Chanley, J. D., Feageson, E., *J. Am. Chem. Soc.* 77, 4002 (1955).
(2) Chanley, J. D., Gindler, E. M., *Ibid.*, 75, 4035 (1953).
(3) Chanley, J. D., Gindler; E. M., Sobotka, H., *Ibid.*, 74, 4347 (1952).
(4) Courtney, R. C., Gustafson, R. L., Chaberek, S., Jr., Martell, A. E., *Ibid.*, 81, 519 (1959).
(5) Courtney, R. C., Gustafson, R. L., Westerback, S. J., Hy,tiainen, H., Chaberek, S. C., Martell, A. E., *Ibid.*, 79, 3030 (1957).
(6) Gustafson, R. L., Chaberek, S. C., Martell, A. E., *Ibid.*, in press.
(7) Gustafson, R. L., Martell, A. E., *Ibid.*, 81, 525 (1959).
(8) *Ibid.*, 84, 2309 (1962).
(9) Hofstetter, R., Murakami, Y., Mont, G. E., Martell, A. E., *Ibid.*, 84, 3041 (1962).
(10) Mont, G. E., Martell, A. E., unpublished results, Ph.D. thesis, Clark University, 1962.
(11) Murakami, Y., Martell, A. E., *J. Am. Chem. Soc.*, in press.

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12

Effects of Metal Ions on Imidazole Catalysis of the Mutarotation of Glucose

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The rates of mutarotation of glucose in the absence and presence of imidazoles and metal ions have been measured at 25° and pH 4 to 7. Under the experimental conditions, only the imidazole free bases serve as catalysts, and the rate constants of mutarotation obey the equations $k = 0.0104 + 1.14$ (imidazole) and $k = 0.0104 + 0.14$ (benzimidazole). The difference in catalytic coefficients is related to the difference in pK's. In the presence of metal ions which complex with the imidazoles, the rates of mutarotation decrease because of decrease in the concentration of imidazole free base. The concentrations of the latter derived from kinetic data, agree with values calculated from equilibrium pH data. Glucosamine hydrochloride is glucose with a hydroxyl group replaced by $-NH_3^+$. From pH 4 to 7, the basic amino group in glucosamine serves as an intramolecular catalyst. In the presence of metal ions, rates of mutarotation decrease; the effect of metal complexation is smaller for glucosamine than for intermolecular catalysis by imidazole. A mechanism for the intramolecular catalysis of mutarotation is proposed.

Gurd *et al.* (*8*) have measured the reactivity of imidazole kinetically by its ability to catalyze the hydrolysis of *p*-nitrophenyl acetate in the absence and presence of Zn(II) or Cu(II) ion. The interaction between imidazole and metal ions was determined from the rate data and from equilibrium pH values; the two methods of measuring the concentration of imidazole free base are mutually compatible. A similar study is reported here on the ability of imidazole and benzimidazole to catalyze the mutarotation of D-glucose in the absence and presence of Ni(II), Cd(II), and Ca(II) ions. The metal ions themselves at a concentration of 0.02*M* do not catalyze the mutarotation and the decrease in the rate of imidazole catalysis in the presence of metal ions is due to interaction between imidazole and metal ions. The concentrations of imidazole and benzimidazole free base calculated from the rate data are in satisfactory agreement with the concentrations derived from equilibrium pH data. The results of an intramolecular catalysis of mutarotation and of the metal ion effects are presented.

Experimental

Materials. Imidazole, benzimidazole, and glucosamine hydrochloride were obtained from the Eastman Kodak Co., and used without further purification, after drying for several days over anhydrous calcium chloride. Stock solutions of nickel nitrate and nickel chloride were analyzed by precipitation with dimethylglyoxime. Stock solutions of cadmium nitrate were analyzed gravimetrically by conversion to cadmium sulfate.

Measurement. Rotations were measured with a Rudolph Model 200 photoelectric polarimeter operating from a sodium vapor lamp. Water was circulated through 20-cm. tubes with glass end plates, from a bath maintained at 25.0° ± 0.1°. The runs on the mutarotation of D-glucose showed excellent first-order dependence over two half lives. In studies on the mutarotation of glucosamine hydrochloride in the presence of varying concentrations of sodium hydroxide and metal salt, it was necessary to add the alkali first, then the metal salt, to avoid precipitation.

Results and Discussion

The rate constant, *k*, of mutarotation is given by the equation

$$k = \frac{1}{t}\log_{10}\frac{(R_0 - R_\infty)}{(R_t - R_\infty)} \tag{1}$$

where *t* is time in minutes, and R_0, R_∞, and R_t are the initial angle of rotation, the final equilibrium angle, and the angle at time *t*, respectively. Plots of log $(R_t - R_\infty)$ *vs.* *t* give straight lines and the rate constant, *k*, is reproducible to ±2%.

The rates of mutarotation of glucose, in the presence of 0 to 0.238*M* imidazole and of 0 to 0.230*M* benzimidazole at 25°, have been measured; the rate constant data are given in Table I. Linear plots of the observed rate constants for glucose *vs.* the molarity of imidazole or benzimidazole (Im or BIm) are obtained. The straight lines follow the equations

$$k = k_0 + k_{\text{Im}}(\text{Im}) \qquad (2$$

$$k = k_0 + k_{\text{BIm}}(\text{BIm}) \tag{3}$$

where k and k_0 are in min.$^{-1}$ and k_{Im} and k_{BIm} are the catalytic coefficients of the free bases, imidazole and benzimidazole, respectively, in liters per mole minute. The values of k_{Im} and k_{BIm} are listed in Table I.

A plot of the observed rate constants for glucose with T_{Im}, the total concentration of imidazole, does not yield a straight line. This is shown by the values of k' listed in Table I, where

$$k' = (k - k_0)/T_{\text{Im}} \tag{4}$$

The constancy of the values of k_{Im} and k_{BIm}, rather than the values of k', in Table I suggests that the basic form of imidazole or benzimidazole is the catalytic species, and that the imidazolium or benzimidazolium ion is not. This interpretation is in agreement with that of Gurd (*8*) and of Bruice and Schmir (3) on the catalyzed hydrolysis of *p*-nitrophenyl acetate by imidazole. Brönsted and Guggen-

Table I. Imidazole Catalysis of Mutarotation of D-Glucose, 0.27*M*, 25°

A. Imidazole, $pK_A = 7.08$

(*Im*), *M*	(*HIm*$^+$), *M*	*k*	k_{Im}	*k'*
0.000	0.000	0.0104		
0.030	0.150	0.0458	1.18	0.20
0.040	0.079	0.0568	1.16	0.39
0.050	0.150	0.0667	1.13	0.28
0.080	0.158	0.0977	1.09	0.37
		Av.	1.14	

B. Benzimidazole, $pK_A = 5.53$

(*BIm*)	(*HBIm*$^+$)	*k*	k_{BIm}	*k'*
0.000	0.000	0.0104		
0.025	0.075	0.0138	0.14	0.03
0.0375	0.0375	0.0161	0.14	0.08
0.050	0.150	0.0171	0.13	0.03
0.080	0.150	0.0125	0.14	0.05
		Av.	0.14	

heim (2) have given values for the catalysis of the mutarotation of glucose by acids and have shown that the acid catalytic constant, k_A, increases with increase in the acid dissociation constant, K_A. These authors list for trimethylacetic acid: $K_A = 10^{-5}$, $k_A = 2 \times 10^{-3}$. Since the values of K_A for imidazole and benzimidazole are much smaller, 8×10^{-8} and 3×10^{-6}, respectively, their acid catalytic constants would be expected to be smaller than 10^{-3}. Any catalysis by the imidazolium or benzimidazolium ion therefore would be undetected.

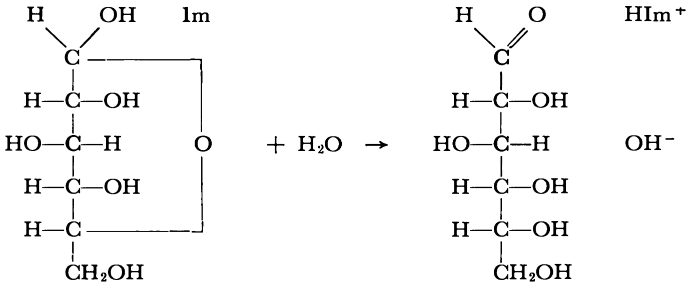
Bruice and Schmir (3) have shown that for a series of imidazole derivatives, k_{Im} depends on the base strength of the catalyst and since pK_A is an approximate measure of base strength, the value of k_{Im} should increase with increase in pK_A. Table I shows that this is indeed the case. Imidazole, $pK_A = 7.08$, has a catalytic constant eight times larger than that of benzimidazole, $pK_A = 5.53$. Brönsted and Guggenheim (2) have obtained a linear relationship between log k_B and pK_A for a series of carboxylic acids in the pK_A range of 2 to 5, where k_B is the carboxylate anion basic catalytic constant for the mutarotation of glucose and K_A is the acid dissociation constant of the acid. Our results for imidazole and benzimidazole fit fairly well into the Brönsted plot.

For the mutarotation of glucose in aqueous media and at 25°, Li *et al.* (*12*) obtained the equation $k = 0.0102 + 0.283\ (H^+)$, while Kuhn and Jacob's equation (9) is $k = 0.0104 + 0.334\ (H^+)$ and Hudson's equation (6) is $k = 0.0096 + 0.258\ (H^+)$. The pH range of the experimental solutions listed in Table I is from 4.85 to 6.8, and it is obvious that the catalytic effect of hydrogen ion in our experiments is entirely negligible. Using imidazole and benzimidazole as catalysts, our equations are:

$$k = 0.0104 + 1.14\,(\text{Im}) \tag{5}$$

$$k = 0.0104 + 0.14\,(\text{BIm}) \tag{6}$$

A scheme for the imidazole catalysis of the mutarotation of glucose, similar to the "concerted" mechanism proposed by Swain and Brown (*13*), is shown below, in which a proton is transferred from the D-glucose to imidazole or benzimidazole and from the H_2O (represented as an acid) to the D-glucose in the rate-determining step.



(7)

However, the mechanism given in Equation 7 is not necessarily the correct one. Eigen and Maass (*4*, *5*) have found that the reaction between glucose and imidazole to yield imidazolium and glucose anion has a second-order rate constant of $10^5\ M^{-1}$ sec.$^{-1}$, while the rate constant for the reverse reaction is 2×10^{10} M^{-1} sec.$^{-1}$ Thus the ionization equilibrium is established before mutarotation of glucose can occur, and it is possible that the catalytic action of imidazole involves the pre-equilibrium between glucose and imidazole, forming the imidazolium cation and glucose anion, and the subsequent reaction between them (*7*). However, the reaction of glucose anion with imidazolium ion cannot be distinguished stoichiometrically from a reaction between glucose and imidazole.

The effects of metal ions on imidazole and benzimidazole catalysis of the mutarotation of glucose are shown in Tables II and III, respectively. The concentration of imidazole (Im) or benzimidazole (BIm) free base is calculated in two ways: from pH of the experimental solution and the pK_A of the imidazole, and from the rate constants using Equation 5 or 6. It is seen, by comparing columns 6 and 7 of Tables II and III, that the concentration of imidazole or benzimidazole free base calculated from the rate data is in good agreement with the concentration calculated from the equilibrium pH data. In the calculation from rate data, it is assumed that the metal ions, M^{+2}, and the (metal-imidazole)$^{+2}$ complexes do not catalyze the mutarotation of glucose. The former assumption was tested by measuring the rate of mutarotation of glucose in 0.01*M* $Ni(NO_3)_2$, and in 0.01*M* $Ca(NO_3)_2$. The rate constants in these media are 0.0104 and 0.0105, respectively, essentially the same as in pure water.

From the increase in pH and rate constant [with consequent increase in free (Im)] in going from experiment 1 to 4 in Table II, it is seen that the stability of the imidazole complexes is in the order: $Ni^{+2} > Cd^{+2} \gg Ca^{+2}$. This is in agreement with the order of formation constants of these complexes (*1*), and with the finding (*11*) that there is no appreciable interaction between calcium ion and imidazole. Moreover, in a solution with an initial composition of 0.238*M* imidazole and 0.158*M* HCl, *k* was found to be 0.0977 min.$^{-1}$ (Table I), so that the increase in *k* for this solution in the presence of 0.020*M* $Ca(NO_3)_2$ (experiment 4 in Table II) amounts to only 3.6%.

Tables II and III demonstrate abundantly that in a given medium the rate constant and pH decrease (with accompanying decrease in the concentration of free imidazole or benzimidazole) with increase in concentration of metal ion. This is as expected, because there is greater complexation in a given medium when the concentration of the metal ion increases.

The metal complex of benzimidazole is much less stable than the corresponding complex of imidazole. Thus a comparison of experiment 1 in Table II and experiment 1 in Table III shows that starting with equal concentrations of the uncharged ligand, the ratios of the complexed ligand per mole of Ni(II) are equal

Table II. Effects of Metal Ions on Imidazole Catalysis of Mutarotation of Glucose at 25°

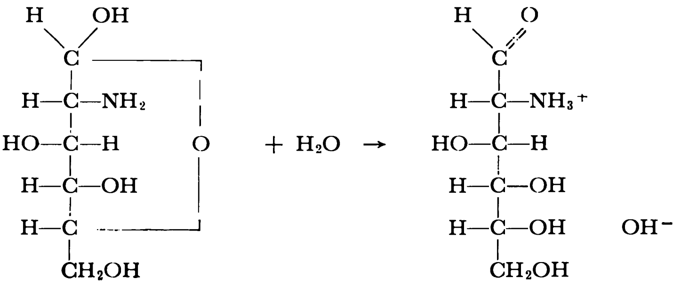
	Initial Total Concn.					*(Im)*	
Expt. No.	*Metal salt*	*Imidazole*	*HCl*	*pH*	*k, Min.*$^{-1}$	*From pH*	*From rates*
1	$Ni(NO_3)_2$, 0.020M	0.238	0.158	6.28	0.0389	0.025	0.025
2	$NiCl_2$ 0.020	0.238	0.158	6.29	0.0413	0.026	0.027
3	$Cd(NO_3)_2$, 0.020	0.238	0.158	6.45	0.0532	0.037	0.037
4	$Ca(NO_3)_2$ 0.020	0.238	0.158	6.78	0.1013	0.079	0.080
5	$NiCl_2$, 0.006	0.238	0.158	6.67	0.0785	0.061	0.060
6	$Cd(NO_3)_2$ 0.006	0.238	0.158	6.70	0.0851	0.066	0.066
7	$Ni(NO_3)_2$ 0.010	0.150	0.120	5.90	0.0223	0.008	0.010
8	$Ni(NO_3)_2$ 0.007	0.150	0.120	6.11	0.0273	0.013	0.015

Table III. Effect of Ni(II) on Benzimidazole Catalysis of Mutarotation of Glucose at 25°

	Initial Total Molar Concn.					*(BIm)*	
Expt. No.	$Ni(NO_3)_2$	*Benzimidazole*	*HCl*	*pH*	*k, Min.*$^{-1}$	*From pH*	*From rates*
1	0.020	0.230	0.150	5.10	0.0184	0.056	0.057
2	0.010	0.230	0.150	5.20	0.0200	0.070	0.069
3	0.020	0.200	0.150	4.84	0.0149	0.031	0.032
4	0.010	0.200	0.150	4.95	0.0164	0.040	0.043
5	0.010	0.150	0.100	5.15	0.0160	0.042	0.040
6	0.020	0.120	0.090	4.78	0.0129	0.016	0.018

to 2.75 and 1.15, respectively, for the imidazole and benzimidazole complexes. Lane and Quinlan (*10*) carried out pH titration of benzimidazole in the presence of Ni(II), and reported that they could not study the complexation because of hydrolysis of the metal ion. In our experiments the pH values are low enough so that the Ni(II) ion did not hydrolyze. The weaker complex-forming ability of benzimidazole, as compared with imidazole, may be ascribed to the smaller pK_A and possible steric hindrance in the former ligand.

Glucosamine hydrochloride is glucose with the hydroxyl group on carbon atom 2 replaced by $-NH_3^+$. When an alkali is added to an aqueous solution of glucosamine hydrochloride, glucosamine is produced, and the basic amino group acts as an intramolecular catalyst for the mutarotation of glucose. The results are shown in Table IV. The rate constant of mutarotation of glucosamine is a linear function of the sodium hydroxide concentration; in each run 0.500 gram of glucosamine hydrochloride is added to 10 ml. of the alkali solution. The pH values for the experimental solutions vary from 3.8 to 6.6 and, in this range, hydrogen or hydroxyl ion catalysis should be negligible. The basic amino group in glucosamine therefore is the intramolecular catalyst and the data show that the $-NH_3^+$ is not a catalytic species. A mechanism for the intramolecular catalysis may be represented by Equation 8:



(8)

It is easy to see from Equation 8 why $-NH_3^+$ ion does not catalyze the mutarotation: The positively charged ion cannot extract the proton from the hydroxyl group on carbon 1. When no NaOH is added, in the presence of 0.0114*M* $Cd(NO_3)_2$, the rate constant of mutarotation is 0.0122, practically the same as in the absence of the metal. This is as expected, since no glucosamine complex is present.

Table IV. Mutarotation of Glucosamine at 25°

(0.500 gram of glucosamine hydrochloride in 10 ml. of sodium hydroxide solution)

$c_{NaOH} = c_{glucosamine}$	k, *Min.*$^{-1}$
0.0000 *M*	0.0125
0.0202	0.0221
0.0364	0.0302
0.0479	0.0382

The catalysis of mutarotation of glucosamine hydrochloride involves an intramolecular mechanism, and so the catalytic coefficient of glucosamine, k_{GlNH_2}, must have the dimension, min.$^{-1}$, instead of liters/mole min. The total rate is then

$$kT = 0.0125\,(GlNH_3^+) + k_{GlNH_2}\,(GlNH_2) \tag{9}$$

where T is total concentration and, in the absence of complexing metal ion, is equal to the sum of the concentrations of glucosamine hydrochloride ($GlNH_3^+$) and glucosamine ($GlNH_2$). In Table IV, $T = 0.2319M$ and the average value of k_{GlNH_2} is 0.13 min.$^{-1}$. With this value of k_{GlNH_2}, Equation 9 becomes

$$\begin{aligned} k &= \frac{0.0125\,(T - (GlNH_2))}{T} + \frac{0.13\,(GlNH_2)}{T} \\ &= 0.0125 + \frac{0.12\,(GlNH_2)}{T} \end{aligned} \tag{10}$$

For the data of Table IV, the values of k calculated from Equation 10 agree with the observed k within about 3%. Equation 10 further predicts that at constant sodium hydroxide concentration ($T >$ NaOH), an increase in T would be accompanied by a decrease in k, and this has been experimentally observed.

If the last solution in Table IV contains in addition 0.0229*M* $Cd(NO_3)_2$ or $NiCl_2$, the rate constant drops to 0.0317 and 0.0278 min.$^{-1}$, respectively. Using Equation 10, it can be calculated that in the presence of 0.0229*M* Cd(II) and Ni(II), the concentration of glucosamine free base drops from 0.0479*M* to 0.0371 and 0.0296 *M*, respectively. A comparison of these data with experiments 2 and 3 of Table II shows clearly that the effects of metal ions on intramolecular catalysis of the mutarotation of glucosamine hydrochloride are less than the corresponding effects on the intermolecular imidazole catalysis of the mutarotation of glucose.

By a pH titration method, we have obtained log $K_1 = 2.0$ and 2.5, respectively, for the formation constants of the 1 to 1 Cd and Ni complexes of glucosamine. These values are about 0.7 log unit lower than the corresponding metal complexes of imidazole (*1*), so that the metal ions would bind glucosamine less strongly than imidazole, and hence would exert a smaller effect. Moreover, in intramolecular catalysis, the catalytic amino group is already part of the glucose molecule, so that the catalytic influence would probably be relatively less affected by the presence of a metal ion than in the case of intermolecular catalysis. Our data also show that Ni(II) has a greater effect on intramolecular catalysis than Cd(II), and this is the same order as has been observed for intermolecular catalysis.

Acknowledgment

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Literature Cited

(1) Bjerrum, J., Schwarzenbach, G., Sillén, L. G., "Stability Constants," Spec. Pub. 6, Part I, "Organic Ligands," Chemical Society, London, 1957.
(2) Brönsted, J. N., Guggenheim, E. A., *J. Am. Chem. Soc.* **49,** 2554 (1927).
(3) Bruice, T. C., Schmir, G. L., *Ibid.,* **79,** 1663 (1957).
(4) Eigen, M., Baker Lectures 1961/62, Cornell University, Ithaca, N. Y.
(5) Eigen, M., Maass, G., private communication.
(6) Hudson, C. S., Sawyer, H. L., *J. Am. Chem. Soc.* **39,** 470 (1917).
(7) Kilde, G., Wynne-Jones, W. F. K., *Trans, Faraday Soc.* **49,** 243 (1953).
(8) Koltun, W. L., Dexter, R. N., Clark, R. E., Gurd, F. R. N., *J. Am. Chem.* Soc. **80,** 4188 (1958).
(9) Kuhn, R., Jacob, P., *Z. physik. Chem.* **113,** 389 (1924).
(10) Lane, T. J., Quinlan, K. P., *J. Am. Chem. Soc.* **82,** 2994 (1960).
(11) Li, N. C., Chu, T. L., Fujii, C. T., White, J. M., *Ibid.,* **77,** 859 (1955).
(12) Li, N. C., Kaganove, A., Crespi, H. L., Katz, J. J., *Ibid.,* **83,** 3040 (1961).
(13) Swain, C. G., Brown, J. F., *Ibid.,* **74,** 2534, 2538 (1952).

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Cobalt-Catalyzed Cleavage of *N-Hydroxyethylethylenediamine* to Ethylenediamine in the Presence of Oxygen

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Oxidation of cobalt(II) to cobalt(III) by oxygen in the presence of *N*-hydroxyethylethylenediamine and carbon produces large amounts of ethylenediamine. Other products are formaldehyde, formic acid, and ammonia. The sum of the moles of ethylenediamine and ammonia produced is equal to the total number of moles of cobalt(II) oxidized. A steady-state concentration of Co(II)-Co(III) is established in which the ratio Co(III)/Co(II) = 1.207. Thus cobalt ion behaves as a true catalyst for cleavage of the *N*-hydroxyethylethylenediamine. The total amount of cobalt(II) oxidized per unit time, *X*, was calculated from the derived equation: $X = 3.8 + 7.0\ k_2T - 3.8e^{-2.2k_2t}$, where $k_2 = 0.65$ hr.$^{-1}$ The observed rate of formation of ethylenediamine plus ammonia also follows this equation. It is proposed that the cobalt ion serves as a center where a superoxide ion [derived from oxidation of cobalt(II) by oxygen] and the ligand are brought together for reaction.

One of the most widely used methods for the formation of cobalt(III) complexes involves the oxidation of a cobalt(II) salt by oxygen in the presence of a ligand. Generally, activated carbon is added as a catalyst. This experimental procedure was reported to be useful for the preparation of tris-*N*-hydroxyethylethylenediamine cobalt(III) chloride (*15*). The same procedure was used by other workers to obtain this complex for a study of physical properties (*16*). In the study it was noted that the complex possessed properties remarkably similar to those of trisethylenediamine cobalt(III) chloride. Subsequently, it was shown (*6*) that ethylenediamine is formed during the reaction and that trisethylenediamine cobalt(III) chloride may be isolated. The purpose of the present investigation was to elucidate the nature of this cleavage reaction and to obtain a quantitative relationship between the amount of cobalt(II) oxidized and the amount of ethylenediamine formed.

Products of the reaction have been identified as ethylenediamine, formaldehyde, formic acid, and ammonia. A kinetic evaluation of rate experiments indicates that for each cobalt(II) ion oxidized either one molecule of ethylenediamine or one molecule of ammonia appears.

Experimental

Materials. *N*-Hydroxyethylethylenediamine (2,2-aminoethylaminoethanol), Eastman White Label, was purified by vacuum distillation from calcium hydride (b.p. 88° C. at 1 mm. Hg). Only the middle fraction was retained.

Commercial oil-pumped nitrogen was freed of oxygen by passing the gas through a chromium(II) solution (*27*).

Apparatus. Experiments were carried out in a 250-ml. round-bottomed, three-necked flask, fitted with a gas inlet tube, a sample dip tube, and a gas exit tube fitted with a reflux condenser. Exit gas was passed through traps of standard sulfuric acid to remove any basic gases.

A Beckman Model DU spectrophotometer was used for the spectrophotometric determination of cobalt(II).

Reaction Conditions. Unless otherwise stated, all reactions contained 4.76 grams (0.020 mole) of $CoCl_2.6H_2O$, 52.05 grams (0.500 mole) of *N*-hydroxyethylethylenediamine, 1.0 ml. of 12*N* hydrochloric acid, 100 ml. of water, and 2.5 grams of activated carbon. The temperature of the solution was maintained at 96–8° C., and air was passed through the solution at a rate of 100 ml. per minute.

Identification of Reaction Products. Carbon dioxide–free air was bubbled through the previously described reaction mixture. At the end of 6 hours, the carbon was removed by filtration, and the filtrate poured slowly into six times its volume of ethanol (95%). The precipitate which formed was recrystallized first from an ethanol-water solution and finally from a minimum amount of water.

ANALYSES. Calcd. for $CoC_6H_{24}N_6Cl_3$: C, 20.8; H, 7.0; Cl, 30.7. Found: C, 20.7; H, 7.0; Cl, 31.3.

Ethylenediamine was determined quantitatively on the product by the salicylaldehyde method (*14*). The product was found to contain 50.1% ethylenediamine compared with a theoretical composition of 52.3% for $[Co(en)_3]Cl_3$.

Experiments to determine the other reaction products were performed in two ways: (1) Qualitative tests were made on the reaction solution after the 6-hour reaction period and after removal of carbon but before precipitation of the $[Co(en)_3]Cl_3$ by ethanol; and (2) after cobalt was removed from the reaction solution by precipitation with hydrogen sulfide and the solution boiled to remove hydrogen sufide. Tests were made for ethylene glycol, glycolic acid, oxalic acid, carbon dioxide, and carbon monoxide with negative results. The effluent gas from the reaction was checked for carbon monoxide and carbon dioxide, again with negative results.

The test for ethylene glycol was performed by oxidation of the sample with periodic acid and detection of the resulting formaldehyde with fuchsin–sulfurous acid reagent (*9*).

Two tests were used for the detection of glycolic acid: the chromatropic acid test and the method whereby the glycolic acid is treated with sulfuric acid and the resulting carbon monoxide detected by phosphomolybdic acid–palladium chloride reagent (*10*, *12*).

The aniline blue test was used for the detection of oxalic acid (*13*).

The phosphomolybdic acid–palladium chloride test was used for the detection of carbon monoxide (*25*).

Carbon dioxide was determined gravimetrically with Ascarite.

The reliability of the tests for ethylene glycol, glycolic acid, and carbon monoxide were verified by adding known amounts of these materials to the reaction solution.

A portion of the reaction solution was acidified with sulfuric acid and steam-distilled into sodium hydroxide solution. The distillate was found to contain formaldehyde and formic acid. The formaldehyde was identified by precipitation with dimedone (*31*). The precipitate had a melting point of 186.0–86.5° C. as compared with a literature value of 187° C. (*17*). The formic acid in the distillate was identified by first removing the formaldehyde with dimedone and then reducing the formic acid to formaldehyde with magnesium (*11*). The dimedone precipitate of this formaldehyde had a melting point of 185.3–6.5° C.

The effluent gas from the reaction was passed through a 0.1*N* hydrochloric acid solution; the solution was evaporated to dryness, and the resulting salt was shown by analysis to be ammonium chloride.

Experiment 1. Effect of Carbon Catalyst on Oxidation of Cobalt(II) to Cobalt(III) and Formation of Ethylenediamine and Effect of Cobalt on Formation of Ethylenediamine. Carbon dioxide-free air was bubbled through the reaction mixture. Nine determinations each of the amounts of ammonia volatilized, the ethylenediamine concentration, and the cobalt(II) concentration were made over a period of 18 hours. The results are shown in Figure 1.

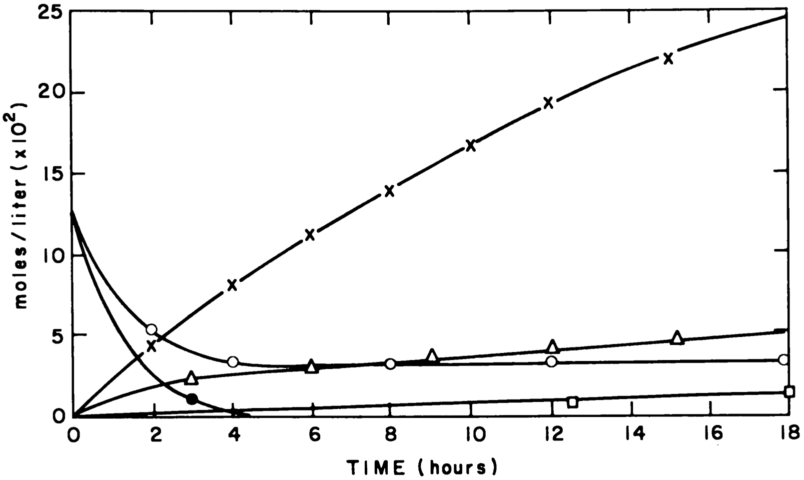


Figure 1. Charge of concentration in air at 95° C.

X *Ethylenediamine, carbon present*
△ *Ethylenediamine, no carbon present*
● *Cobalt(II), carbon present*
○ *Cobalt(II), no carbon present*
□ *Ethylenediamine, carbon but no cobalt ion present*

The amount of ammonia volatilized was determined from the amount of standard sulfuric acid consumed in the traps. Ethylenediamine was determined by the salicylaldehyde method (*14*). The sample for cobalt(II) determination was made slightly acidic with hydrochloric acid immediately upon removal of the sample from the reaction flask, in order to prevent further oxidation of the cobalt (*18*). The carbon was removed by filtration, and the cobalt(II) concentration was determined spectrophotometrically as the cobalt–ammonium thiocyanate complex, $(NH_4)_2Co(NCS)_4$ (*28*).

The experiment was repeated with no carbon present. The results of this experiment are also shown in Figure 1. The reaction was repeated again with no cobalt or hydrochloric acid present (Figure 1).

Experiment 2. Step Involving Ligand Cleavage and Attempt to Detect Reaction Intermediate. Oxygen-free nitrogen was bubbled through the reaction mixture. Two samples were taken at 20-minute intervals for cobalt(II) and ethylenediamine analysis to make certain that no reaction was occurring. Immediately after the second sample was taken, the flow of air through the sample solution was begun and maintained for 20 minutes. Then the air flow was replaced by the nitrogen flow. A sample for cobalt(II) and ethylenediamine analysis was taken immediately at the end of the air flow, followed by two more samples at 20-minute intervals while the nitrogen flow was continuing. Once again air was introduced for 20 minutes, and the same procedure was repeated. The data from this experiment are plotted in Figure 2.

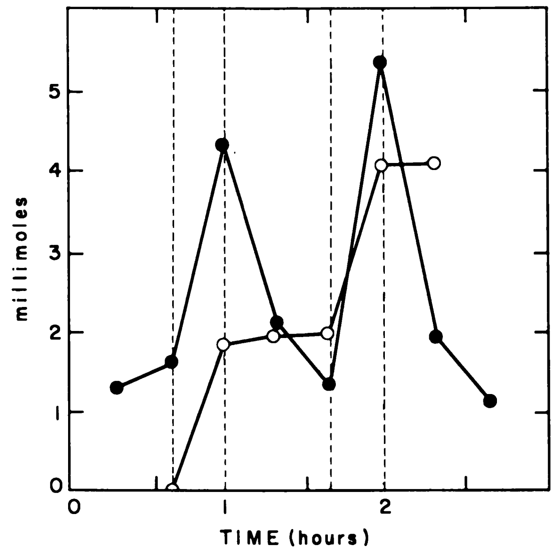


Figure 2. Effect of air on formation of ethylenediamine and cobalt(III) concentration

○ *Ethylenediamine*
● *Cobalt(III)*

Experiment 3. Rates of Formation of Ethylenediamine and Ammonia *vs.* Rate of Disappearance of Cobalt(II). Carbon dioxide-free air was bubbled through the solution. Ammonia, ethylenediamine, and cobalt(II) were determined periodically over a total reaction time of 5 hours. The results of this experiment are collected in Table I and plotted in Figure 3. The ammonia measured was actually the ammonia volatilized during the reaction, but it was calculated as moles per liter of solution in order to be consistent with the ethylenediamine and cobalt(II) results.

Table I. Formation of Ethylenediamine and Ammonia and Disappearance of Cobalt(II)

(From Experiment 3)

Reaction Time, Hours	*Ethylenediamine, Moles/Liter × 10^2*	*Ammonia, Moles/Liter × 10^2*	*Cobalt(II), Moles/Liter × 10^2*
0.00	0.0	0.0	12.8
0.08	..	..	11.6
0.58	1.8	0.85	9.1
0.95	3.6	1.72	7.4
1.32	4.7	2.50	7.7
1.82	6.7	3.57	5.6
2.48	9.5	5.12	5.8
3.13	11.5	6.09	5.8
3.58	12.9	7.02	..
4.03	14.4	7.73	5.8
4.48	15.8	8.44	..
5.00	17.6	9.38	5.8

Experiment 4. Rates of Formation of Ethylenediamine and Ammonia *vs.* Rate of Appearance of Cobalt(II). Tris-*N*-hydroxyethylethylenediamine cobalt-(III) chloride (*6*) (0.020 mole) was placed in the reaction flask with 100 ml. of water, 45.80 grams of *N*-hydroxyethylethylenediamine, and 2.5 grams of activated carbon, and the reaction was carried out as in Experiment 3. The experimental results are shown in Figure 4.

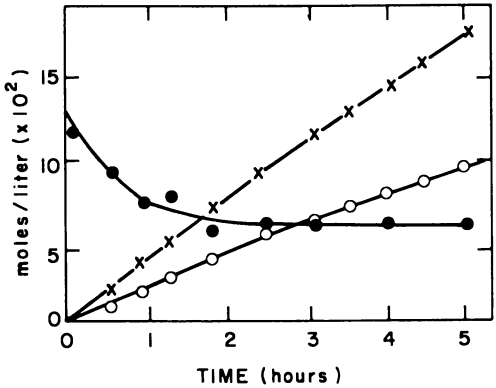


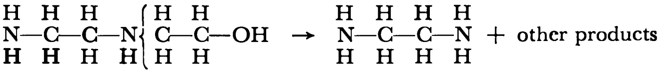
Figure 3. Rates of formation of ethylenediamine and ammonia and rate of disappearance of cobalt(II)

× *Ethylenediamine*
○ *Ammonia*
● *Cobalt(II)*

Experiment 5. Solubility of Ammonia in Reaction Solution. Ammonia was determined on the stream of air leaving the reaction solution. Immediate and complete removal of ammonia from the reaction seemed doubtful. Attempts to determine the amount of ammonia remaining in the reaction solution included gravimetric analysis with sodium cobaltinitrite and sodium tetraphenyl boron, volatilization or distillation techniques, etc., without success. The amount of ammonia "holdup" in the solution was estimated by sweeping an initially ammonia-free reaction solution identical with the starting solution in Experiment 3 with nitrogen containing a known amount of ammonia. By analyzing the gas coming from the solution for ammonia, it was determined that after about $^3/_4$ hour a constant amount of ammonia (0.8 meq.) is held by the reaction solution. Corrections for this holdup were made in the final data.

Discussion

The formation of ethylenediamine from the *N*-hydroxyethylethylenediamine must occur through rupture of the carbon-nitrogen bond between the hydroxyethyl group and the secondary nitrogen as follows:



$$\begin{array}{cccccccccccccccccccc}
\mathrm{H} & & \mathrm{H} & & \mathrm{H} & & & & \mathrm{H} & & \mathrm{H} & & & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & \\
\mathrm{N} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{N} & \{ & \mathrm{C} & - & \mathrm{C} & - & \mathrm{OH} & \rightarrow & \mathrm{N} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{N} & + \text{ other products} \\
\mathrm{H} & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & & & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} &
\end{array}$$

The formaldehyde and formic acid detected in the reaction solution were derived from the hydroxyethyl group which is split off in the formation of ethylenediamine. The fact that no two-carbon derivatives of the hydroxyethyl group (ethylene glycol, glycolic acid, etc.) were detected indicates that oxidative cleavage of the hydroxyethyl group occurs simultaneously with the cleavage of the carbon-nitrogen bond between the hydroxyethyl group and the secondary nitrogen. All two-carbon fragments were shown to survive in synthetic reaction mixtures. The presence of formic acid in the reaction mixture does not necessarily mean that formic acid is a product of the cleavage of the carbon-carbon bond of the hydroxyethyl group. Rather, both carbon atoms of the hydroxyethyl group may form formaldehyde in a manner similar to the glyco-type cheavage of 2-amino alcohols by periodic acid (*19*), and then because of the oxidizing state of the environment, part of the formaldehyde may be oxidized to formic acid.

The formation of ammonia from the *N*-hydroxyethylethylenediamine during the reaction suggests that some additional reaction product is formed. From a consideration of the mechanism proposed, one would postulate that this reaction product is ethanolamine. Efforts to detect this compound were unsuccessful because of the large concentration of *N*-hydroxyethylethylenediamine.

Figure 1 shows the effect of cobalt and activated carbon on the rate of formation of ethylenediamine from *N*-hydroxyethylethylenediamine upon aeration of a hot aqueous solution. When both cobalt and carbon are present in the reaction solution, the rate of formation of ethylenediamine is approximately five times greater than when cobalt is present but carbon is absent, and about 19 times greater than when cobalt is absent and carbon is present.

Experiment 1 reveals an important difference in the behavior of the cobalt(II) concentration in the presence and absence of carbon. In the absence of activated carbon the cobalt(II) was completely oxidized to cobalt(III) by the air stream in 4 hours. However, when activated carbon was present in the reaction solution, the cobalt(II) concentration reached a steady-state value of approximately one fourth of the initial cobalt(II) concentration.

The possibility was considered that a reaction intermediate may be formed during the reaction, with a lifetime sufficiently long (about 5 minutes or more) to be easily detected. Accordingly, Experiment 2 was performed to detect this intermediate. As can be seen from Figure 2, ethylenediamine forms while the solution is aerated, but upon switching from a stream of air to a stream of oxygen-free nitrogen, the ethylenediamine formation stops immediately. This behavior indicates that a relatively long-lived intermediate does not occur in the reaction, and that no ethylenediamine is produced by reduction of cobalt(III).

Another interesting result was the demonstration that the cobalt(III) formed during the aeration is reduced again to cobalt(II) during the time that the aeration is halted. This is consistent with the finding in Experiment 1, that when activated carbon is present, the cobalt(II) concentration attains a steady-state value. When no carbon is present, the cobalt(II) is essentially all oxidized to cobalt(III).

Figure 4 shows the results of Experiment 4, which was performed to determine if the cobalt(II)-cobalt(III) steady state would be established if the reaction were performed with the cobalt all present initially as cobalt(III). The steady state was established.

Experiment 5 to determine the reliability of the ammonia analyses indicated that after $^3/_4$ hour a constant amount of ammonia (0.8 meq.) was held by the solution. Since the ammonia analyses were performed on the air stream leaving the reaction solution, this indicates that the ammonia analyses would be low by an amount increasing from the start of the reaction to a maximum value of 0.8 meq. in $^3/_4$ hour.

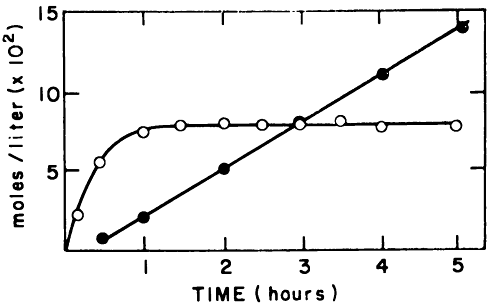


Figure 4. Rate of formation of ethylenediamine and rate of appearance of cobalt(II)

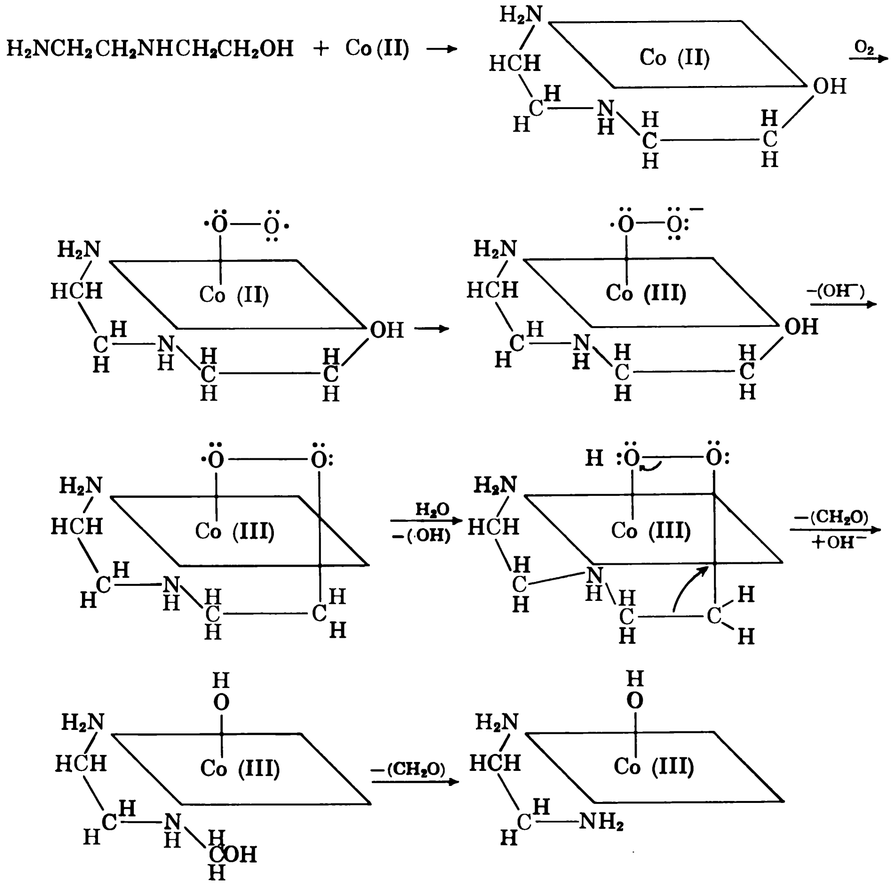
● *Ethylenediamine*
○ *Cobalt(II)*
Ethylenediamine corrected for initial ethylenediamine concentration

Experimental observations indicate that the oxidation of cobalt(II) to cobalt(III) and the formation of ethylenediamine from *N*-hydroxyethylethylenediamine occur simultaneously. This is quite the opposite to what is usually assumed in other instances of transition metal catalysis of organic reactions—for example, the catalytic effect of manganese in the oxidation of oxalic acid (*7, 8*), of iron in the oxidation of cysteine to cystine (*22*) and of thioglycolic acid to dithioglycolic acid (*5, 23*), of copper in the oxidation of pyrocatechol to quinone and in the oxidation of ascorbic acid (*29, 30*), and of cobalt in the oxidation of aldehydes and unsaturated hydrocarbons (*4*). In all these reactions the oxidation of the organic molecule occurs by the abstraction of an electron by the oxidized form of the metal ion.

To explain the simultaneous oxidation of cobalt(II) and the appearance of ethylenediamine, it is proposed that the cobalt(II) functions by bringing the *N*-hydroxyethylethylenediamine and oxygen molecules within reaction proximity. Several investigators have suggested that cobalt(II) may form an addition product with molecular oxygen or the superoxide ion and that this addition product may be an intermediate in cobalt-catalyzed oxidations (*3, 24*). Martell and Calvin (*21*) have proposed that such a complex occurs in the polarography of oxygen in the presence of bissalicylaldethylenediimine complexes of cobalt(II). Basolo and Pearson have pointed out that binuclear peroxo complexes are suggestive of an intermediate addition product of oxygen and the cobalt(II) complex (*2*). The chemistry of the oxygen-carrying complexes such as hemoglobin, hemocyanin, and the cobalt(II) histidine complexes (*1, 20*) lends further support to the existence of such an oxygen-cobalt intermediate.

Although no direct evidence was found in the cobalt–*N*-hydroxyethylethylenediamine reaction that an oxygen-cobalt addition complex was formed, it seems reasonable to postulate that such an intermediate is present in the reaction. An oxygen-cobalt complex intermediate appears to afford the most logical method of explaining the evidence that the oxidation of cobalt(II) to cobalt(III) occurs in conjunction with the oxidative cleavage of the carbon-carbon bond of the hydroxyethyl group and the formation of ethylenediamine.

Based upon the existence of this oxygen-cobalt intermediate, a reaction sequence is proposed for the cobalt(II)-catalyzed conversion of *N*-hydroxyethylethylenediamine to ethylenediamine, which is consistent with the experimental results. The mechanism is a speculation based on the nature of the end products. The stoichiometry of the proposed reaction is :



Ammonia is formed in the reaction. Since the ammonia and ethylenediamine cannot both be formed from the same molecule of *N*-hydroxyethylethylenediamine, the best explanation is that the ammonia is formed by a reaction sequence entirely similar to the mechanism proposed above, except that the oxygen now attacks the carbon adjacent to the primary nitrogen of the ethylenediamine group of the coordinated *N*-hydroxyethylethylenediamine. Such a process would result in formation of ethanolamine. The presence or absence of ethanolamine in the reaction mixture could not be ascertained, because no method was found to detect the predicted amount of ethanolamine in the presence of a much larger amount of *N*-hydroxyethylethylenediamine.

An important feature of the mechanism proposed above is that one cobalt(II) atom is oxidized to cobalt(III) for each molecule of ethylenediamine or ammonia formed. Since the cobalt(III) formed is reduced again to cobalt(II), a steady state is established between cobalt(II) and cobalt(III) concentrations, so that the amount of cobalt(III) present will not be equal to the sum of the amounts of ethylenediamine and ammonia formed. Instead, the sum of the amounts of ethylenediamine and ammonia formed should be equal to the total amount of cobalt(II) oxidized to cobalt(III). The total amount of cobalt(II) oxidized increases continually during the reaction because of the reduction of the resulting cobalt(III) to cobalt(II) in repeating the cycle.

To test the validity of the assumption that one cobalt(II) ion is oxidized to cobalt(III) for each ammonia or ethylenediamine molecule formed, a kinetic expression for the total amount of cobalt(II) oxidized was derived. The values of total cobalt(II) oxidized as calculated from this expression were compared with the experimentally determined sums of the amount of ethylenediamine and ammonia formed.

Because of the complexity of the actual reaction, four simplifying assumptions were made before the derivation was performed.

1. The activity of the oxygen is constant throughout the reaction.
2. The activity of the carbon catalyst is constant throughout the reaction.
3. The *N*-hydroxyethylethylenediamine is present in the reaction solution in sufficient excess so that its concentration may be considered essentially constant for at least the first 5 hours of the reaction.
4. The reaction is assumed to be first order with respect to cobalt(II) concentration.

Based on these assumptions, the reaction can be represented in simplified form as follows:

$$a\mathrm{NH_2CH_2CH_2NHCH_2CH_2OH} + a\mathrm{Co\,(II)} \xrightarrow{k_1}$$
$$b\mathrm{NH_2CH_2CH_2NH_2} + (a - b)\,\mathrm{NH_3} + a\mathrm{Co\,(III)} \quad (1)$$

where $a > b$ and $\mathrm{Co\,(III)} = \mathrm{NH_2CH_2CH_2NH_2} + \mathrm{NH_3} = b + (a - b) = a$

$$\mathrm{Co\,(III)} \xrightarrow{k_2} \mathrm{Co\,(II)} \quad (2)$$

The expression for cobalt(II) concentration at time t was derived as follows:
Let A = cobalt(II) concentration
B = cobalt(III) concentration
A_0 = initial cobalt(II) concentration
B_0 = initial cobalt(III) concentration
at $t = 0$, $A = A_0$ and $B = B_0 = 0$. Then $B = A_0 - A$

$$\frac{dA}{dt} = -k_1A + k_2B = k_2A_0 - (k_1 + k_2)A \quad (3)$$

Upon integrating and evaluating the integration constant at $t = 0$:

$$A = \frac{k_1A_0e^{-(k_1+k_2)t} + k_2A_0}{(k_1 + k_2)} \quad (4)$$

Using this expression for A, the total amount of cobalt(II) oxidized to cobalt(III) at time t was derived as follows: Let X = total amount of cobalt(II) oxidized to cobalt(III). At $t = 0, X = 0$.

$$\frac{dX}{dt} = k_1A = k_1\left[\frac{k_1A_0e^{-(k_1+k_2)t} + k_2A_0}{(k_1 + k_2)}\right] \quad (5)$$

Integrating, and evaluating at $t = 0$, give

$$X = \frac{k_1^2A_0}{(k_1 + k_2)^2} + \frac{k_1k_2A_0}{(k_1 + k_2)}\,t - \frac{k_1^2A_0}{(k_1 + k_2)^2}\,e^{-(k_1+k_2)t} \quad (6)$$

After the cobalt(II)-cobalt(III) steady state is attained, $dA/dt = 0 = k_1 A_s + k_2 B_s$ from Equation 3. A_s and B_s are the steady-state concentrations of cobalt(II) and cobalt(III), respectively. This expression rearranges to give:

$$\frac{B_s}{A_s} = \frac{k_1}{k_2} = K \qquad B_s = A_0 - A_s \tag{7}$$

Equation 7 can be used to reduce Equations 4 and 6 to the following forms:

$$A = B_s e^{-k_2(B_s/A_s + 1)t} + A_s \tag{8}$$

$$X = \frac{B_s^2}{A_0} + k_2 B_s t - \frac{B_s^2}{A_0} e^{-k_2(B_s/A_s + 1)t} \tag{9}$$

For experiment 3, $A_0 = 12.82 \times 10^{-2}$ mole per liter of cobalt(II), $A_s = 5.81 \times 10^{-2}$ mole per liter of cobalt(III) and, therefore, from Equation 7, $K = 1.207$. Inserting these values into Equations 8 and 9 gives for A, the cobalt(II) concentration, and X, the total amount of cobalt (II) oxidized to cobalt (III)

$$A = 7.0\, e^{-2.2k_2 t} + 5.8 \tag{10}$$

$$X = 3.8 + 7.0\, k_2 t - 3.8\, e^{-2.2k_2 t} \tag{11}$$

The value of k_2 was determined from Equation 10 by the method of least squares (*26*), using the experimental values of A [cobalt(II) concentration] and t in Table I. The result was $k_2 = 0.65$ hr.$^{-1}$ Figure 5 shows the curve for X *vs.* t calculated from Equation 11 using the value $k_2 = 0.65$, compared with the

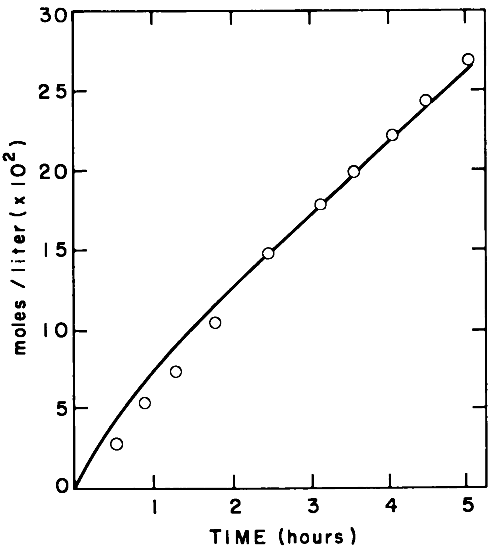


Figure 5. Total amount of cobalt(II) oxidized to cobalt(III) and sum of ethylenediamine and ammonia formed

- ● *Calculated total amount of cobalt(II) oxidized to cobalt(III)*
- ○ *Sum of experimental amounts of ethylenediamine and ammonia formed*

experimentally determined values for the sums of the ethylenediamine and ammonia concentrations (assuming that all the ammonia formed remained in solution). The experimental values for the formation of ethylenediamine and ammonia did not enter into the derivation and evaluation of the theoretical curve.

Figure 5 shows that the experimental sums of ethylenediamine and ammonia formed fall below the theoretical curve during the early stages of the reaction. This discrepancy may be caused by an error in the method of ammonia determination mentioned earlier. The amount of ammonia in the gas stream coming from the reaction solution would be less than the amount of ammonia being formed in the reaction solution during the early stages of the reaction, until the reaction solution becomes saturated with ammonia.

Literature Cited

(1) Bailar, J. C., "Chemistry of the Coordination Compounds," ACS Monograph 131, pp. 45–7, Reinhold, New York, 1956.
(2) Basolo, F., Pearson, R. G., "Mechanisms of Inorganic Reactions," p. 341, Wiley, New York, 1958.
(3) *Ibid.*, pp. 340–1.
(4) Bawn, C. E. H., *Discussions Faraday Soc.* **14**, 181 (1953).
(5) Cannan, R. K., Richardson, G. M., *Biochem. J.* **23**, 1242 (1929).
(6) Drinkard, W. C., Bauer, H. F., Bailar, J. C., Jr., *J. Am. Chem. Soc.* **82**, 2002 (1960).
(7) Duke, F. R., *Ibid.*, **69**, 2885 (1947).
(8) *Ibid.*, p. 3054.
(9) Feigl, F., "Spot Tests in Organic Analysis," pp. 176–7, Elsevier, New York, 1956.
(10) *Ibid.*, p. 329.
(11) *Ibid.*, p. 340.
(12) *Ibid.*, p. 348.
(13) *Ibid.*, p. 355.
(14) Huggins, D., Drinkard, W. C., *Anal. Chem.* **34**, 1756 (1962).
(15) Keller, R. N., Edwards, L. G., *J. Am. Chem. Soc.* **74**, 215 (1952).
(16) Kida, S., Yoneda, H., *Bull. Liberal Arts Coll., Wakayama Univ.* (*Nat. Sci.*) **5**, 9 (1955).
(17) Klein, G., Linser, H., *Mikrochemie* (*Pregl-Festschrift*) **1929**, 204.
(18) Lewis, W. B., Coryell, C. D., Irvine, J. W., Jr., *J. Chem. Soc.* Suppl. Issue **2**, S386 (1949).
(19) Malaprade, M. L., *Bull soc. chim. France* **43**, 683 (1928).
(20) Martell, A. E., Calvin, M., "Chemistry of the Metal Chelate Compounds," pp. 337–80, Prentice-Hall, New York, 1952.
(21) *Ibid.*, pp. 350–52.
(22) Michaelis, L., *J. Biol. Chem.* **84**, 777 (1929).
(23) Schubert, M., *J. Am. Chem. Soc.* **54**, 4077 (1932).
(24) Schumb, W. C., Satterfield, C. N., Wentworth, R. L., "Hydrogen Peroxide," ACS Monograph 128, pp. 642, 661, Reinhold, New York, 1955.
(25) Shepard, M., *Ind. Eng. Chem., Anal. Ed.* **19**, 77 (1947).
(26) Sokolnikoff, I. S., Sokolnikoff, E. S., "Higher Mathematics for Engineers and Physicists," pp. 536–44, McGraw-Hill, New York, 1941.
(27) Stone, H., *J. Am. Chem. Soc.* **58**, 2591–5 (1936).
(28) Tomula, E. S., *Z. anal. Chem.* **83**, 6 (1931).
(29) Weissberger, A., LuValle, J. E., *J. Am. Chem. Soc.* **66**, 700 (1944).
(30) Weissberger, A., LuValle, J. E., Thomas, D. S., Jr., *Ibid.*, **65**, 1934 (1943).
(31) Yoe, J. H., Reid, L. C., *Ind. Eng. Chem., Anal. Ed.* **19**, 77 (1947).

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14

Interaction of Amines and β-Ketoimine–Copper(II) Compounds

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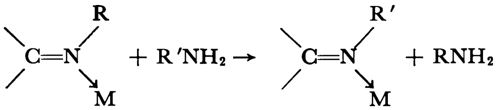
Reactions involving amine exchange of bis-(salicylaldimino)copper(II) compounds and a variety of amines have been reported by other workers. The failure of several β-ketoimine–copper(II) compounds to undergo a comparable reaction is reported here. Several examples of the amine exchange of β-ketoimines in the presence of copper(II) ion are given. The scope and nature of these reactions are discussed, and the anomalous behavior of β-ketoimine–copper(II) compounds is rationalized.

Biologically important reactions such as amination, transamination, and deamination involve intermediate formation of schiff bases, =C=NR, and such reactions frequently involve coordination of this grouping with metal ions (*6*). It is of interest, therefore, to study the reactions of metal complexes of Schiff bases. One reaction, amine exchange, has been reported for bis-(salivylaldimino) copper(II) compounds (*13*, *15*, *17*) but apparently no previous study has been made of the amine-exchange reaction of metal chelates of β-ketoimines, Schiff bases derived from β-diketones. This communication reports the results of such a study.



Experimental

Preparation of Ligands. 4-Iminopentane-2-one was purchased from the Aldrich Chemical Co. and used without further purification.

4-Methyliminopentane-2-one was prepared by the method of Holtzclaw, Collman, and Alire (*7*). The reaction mixture was extracted with ether, and the dried ethereal solution was distilled (b.p. 77–80° 2 mm.; 190–191° at 754 mm.). Reported: b.p. 200° (*9*). An analytical sample was obtained by recrystallization from ether–petroleum ether. White crystals, m.p. 41.2–2.2°. Reported: 40–41° (*7*). Anal: Calcd. for $C_5H_{11}ON$: C, 63.69; H, 9.81. Found: C, 64.01; H, 9.85.

The preparation and properties of 4-phenyliminopentane-2-one have been described (*12*).

Bisacetylacetoneethylenediimine was prepared by a previously described procedure (*10*). M.p. 109–112° (toluene). Reported: 113° (*10*).

4-Butyliminopentane-2-one-butylamine (7.3 grams, 0.1 mole) was added portionwise during a 5-minute period to redistilled acetylacetone (10 grams, 0.1 mole) in an ice-water bath. A white solid formed but melted below room temperature. The reaction mixture was distilled under reduced pressure and a clear, colorless liquid [b.p. 98–105° at 2 mm. (12.9 grams, 83%)] was obtained. A fraction (8.8 grams, b.p. 100–02° at 2 mm., n_D^{25} = 1.5070) was taken as the analytical sample. Anal.: Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04. Found: C, 69.83; H, 10.97.

Salicylanil was prepared by mixing equimolar amounts of salicylaldehyde and aniline and recrystallizing the product from methanol (strong cooling). Short yellow needles formed (67%), m.p. 54–55°. Reported: 51.5° (*1*).

Preparation of Copper(II) Chelates. Bis-(4-iminopentane-2-ono)copper(II) was prepared by a previously described procedure (*1*). Gray needles formed, m.p. (87%) 190–92°. An analytical sample (m.p. 190–92°) was obtained by recrystallization from 95% ethanol. Anal.: Calcd. for $C_{10}H_{16}N_2O_2Cu$: C, 46.22; H, 6.21; N, 10.77. Found: C, 45.61; H, 6.03; N, 10.87.

Bis-(4-phenyliminopentane-2-ono)copper(II) (*7*) was prepared by adding to a solution of the ligand (3.5 grams, 0.02 mole) in 25 ml. of 95% ethanol a solution containing cupric acetate monohydrate (2 grams, 0.01 mole) and 60 drops of concentrated NH_4OH in 30 ml. of water. The dark brown solid that precipitated was filtered off, air-dried, and recrystallized from 95% ethanol. Black crystals formed (54% yield), m.p. 131–33°. Anal.: Calcd. for $C_{22}H_{24}O_2N_2Cu$: C, 64.13; H, 5.87; N, 6.80. Found: C, 63.61; H, 6.06; N, 7.10.

Attempted Preparation of Bis-(4-methyliminopentane-2-ono)copper(II). A solution of the ligand (2.3 grams, 0.01 mole) in 15 ml. of 95% ethanol was added to an ammoniacal cupric acetate solution, which was prepared as in the preceding synthesis. The mixture was heated on a steam bath for about 15 minutes and a gray precipitate formed. The solid was filtered off, washed with water, and dried (yield 1.6 grams), m.p. 185–87° (dec.). Anal.: Calcd. for $C_{10}H_{16}N_2O_2Cu$ (imino derivative), C, 46.22; H, 6.21. Found: C, 46.27; H, 610.

The crude product was recrystallized from 95% ethanol; gray needles formed, m.p. 188–89° (dec.). Anal.: Found: C, 46.91; H, 6.35.

The preparation was repeated using 40 instead of 60 drops of concentrated NH_4OH, and the resulting product was recrystallized from 95% ethanol. Dark-gray needles formed, m.p. 190–91° (dec.). Anal.: Found: C, 52.65; H, 6.27; N, 9.72. Calcd. for $C_{12}H_{20}N_2O_2Cu$(methylimino derivative): C, 50.08; H, 7.00; N, 9.73.

Attempted Preparation of Bis-(4-butyliminopentane-2-ono)copper(11). The procedure was essentially that used for the preparation of the phenylimino derivative, except that the reaction mixture was warmed on a steam bath for 10 minutes. A brown suspension was formed. The mixture was diluted with 100 ml. of water and allowed to stand overnight. The product was collected, air-dried (weight 1.5 grams), and recrystallized from 95% ethanol. Dark-gray needles formed, m.p. 198–99° (dec.). Anal.: Found: C, 46.13; H, 6.58. Calcd. for imino derivative: C, 46.22; H, 6.21.

Bisacetylacetoneethylenediiminocopper(II) was made by the procedure used for the preparation of the phenylimino derivative; 0.01 mole of the ligand dissolved in 10 ml. of 95% ethanol afforded red crystals (88% yield), m.p. 141–44°. Reported (*10*): m.p. 145°.

Bis-[4-(2,6-dimethylphenylimino)pentane-2-ono]copper(II) was prepared by the method described for the phenylimino derivative. Light-brown crystals formed, m.p. 135–37° (95% ethanol). Yield of purified material, 69%. Anal.: Calcd. for $C_{26}H_{33}O_2N_2Cu$: C, 66.56; H, 7.09. Found: C, 66.96; H, 6.99.

Attempted Condensation of Acetylacetone and *N,N*-Dimethyl-1,3-propanediamine. Acetylacetone (5.0 grams, 0.05 mole) and *N,N*-dimethyl-1,3-propanediamine (10.2 gram, 0.1 mole) were dissolved in 100 ml. of methanol. A solution of 5 grams of sodium acetate in 50 ml. of water was added followed by a solution of copper acetate monohydrate (3 grams, 0.015 mole) in 100 ml. of water. The resulting solution was heated with stirring for 30 minutes, then allowed to evaporate for several days. The gray needles which slowly formed were collected and dried (1.5 grams). An analytical sample was obtained upon two recrystallizations from benzene, m.p. 190–93° (dec.). Anal.: Found: C, 46.18; H, 6.18; N, 10.35. Calcd. for bis-(4-iminopentane-2-ono)copper(II): C, 46.22; H, 6.21; N, 10.78. The reaction does not seem to be readily reproducible and is being studied in detail.

Bisacetylacetonetrimethylenediiminocopper (II) was made by the method described for the phenylimino derivative, and using 1.8 grams (0.0.015 mole) of bisacetylacetonetrimethylenediamine, gray crystals (m.p. 180–82°) of bis(4-iminopentane-2-ono)copper(II) could be obtained in nearly quantitative yield. When 40% methylamine was used as the base instead of concentrated ammonia, green platelets (0.6 gram, m.p. 87–92°) of the desired compounds in crude form were obtained. Reported m.p. 97° (*10*).

The filtrate, obtained after the crystals of bis-(4-iminopentane-2-ono)copper (II) were filtered off, was evaporated under reduced pressure. The residue was extracted with water, the extracts were filtered, and the filtrate was treated with sodium hydroxide and *p*-toluenesulfonyl chloride (*18*). In this way, about 30% of the 1,3-propanediamine was accounted for as the crude ditosylate (identity confirmed by lack of freezing-point depression with authentic sample), but only a trace of diamine could be detected in the distillate.

Amine-Exchange Reactions. PROCEDURE A. A solution of a copper compound was heated in 10 ml. of *n*-butylamine or aniline on a steam bath, and, after 30 minutes, the mixture was poured into water. The crystals which formed were filtered off and recrystallized from 95% ethanol.

$Cu[CH_3(C_6H_5N{=})CCH{=}COCH_3]_2 + CH_3(CH_2)_3NH_2$. Starting material was recovered (70%) and recrystallized from 95% ethanol, and its identity confirmed by analysis. Anal.: Found: C, 46.60:H,6.24.

$Cu[CH_3(C_6H_5N{=})CCH{=}COCH_3]_2 + CH_3(CH_2)_3NH_2$. Starting material was recovered (40 to 60%), its identity being confirmed by melting point and absence of depression upon admixture with authentic complex.

$Cu[CH_3CO{=}CHC(CH_3){=}NCH_2 -]_2 + CH_3(CH_2)_3NH_2$. The sole product obtained was identical in every way (color, melting, mixed melting point, infrared spectra) with starting material.

In a subsequent experiment, a nitrogen atmosphere was maintained during the experiment and solvent was removed under reduced pressure. Again, only starting material was recovered.

$CH_3(CH_3N{=})CCH_2COCH_3 + (CH_3(CH_2)_3NH_2$. A solution of the ligand (0.05 mole) in 10 ml. of *n*-butylamine was refluxed for one-half hour and distilled under reduced pressure (2 mm.). The product distilled at 77–80° at 2 mm., as did the pure ligand (recovery =95%). Similarly, only starting material was obtained (95% recovery) when aniline was used instead of *n*-butylamine.

$Cu\{CH_3[2,6(CH_3)_2C_6H_4N{=}]CCHCOCH_3\}_2 + C_6H_5NH_2$. After the reaction solution had been warmed for 20 hours at 100°, the solvent was distilled at reduced pressure. The residue crystallized from 95% ethanol as brown crystals (70% recovery) (m.p. 134–36°), and proved to be unreacted metal-chelate compound.

When the reaction mixture was heated at reflux temperature for 1 hour, considerable reduction (copper mirror) and decomposition occurred. No identifiable product was recovered.

$CH_3(C_6H_5N{=})CCH_2COCH_3 + CH_3(CH_2)_3NH_2$. After a half-hour reflux period, the solvent was removed under reduced pressure and the residual material recrystallized from low-boiling petroleum ether (80% recovery).

o-$HOC_6H_4CH{=}NC_6H_5 + CH_3(CH_2)_3NH_2$. A solution of the Schiff base (0.01 mole) in 20 ml. of *n*-butylamine was refluxed for one-half hour. The solvent was removed under reduced pressure. The product, *o*-$HOC_6H_4CH{=}N(CH_2)_3CH_3$, was obtained as a clear yellow liquid (68%) (b.p. 122–24° at 3 mm.), and its identity confirmed by preparation (*4*) of the copper derivative: green-brown crystals, m.p. 82–3° (methanol). Reported (*4*) m.p.: 80–1°,

$[CH_3(CH_3N{=})CCHCOCH_3]_2Cu + CH_3(CH_2)_3NH_2$. The crude product resulting from attempted amine exchange appears to be impure bis-(4-iminopentane-2-ono)copper(II) on the basis of analysis. Anal: Found: C, 44.18; H, 6.16.

PROCEDURE B. A solution of copper nitrate trihydrate (1.2 grams, 0.005 mole) and excess (200% usually) amine were mixed in 10 ml. of 95% ethanol with a solution of 4-iminopentane-2-one (1.0 gram, 0.01 mole) in 10 ml. of 95% ethanol. The mixture was heated at reflux temperature for 3 to 4 hours, and the resulting solution diluted with water.

Reaction of Ethylenediamine. Using 0.015 mole of diamine, 0.9 gram (61%) of bisacetylacetoneethylenediiminocopper(II) was obtained. Red platelets, m.p. 138–41° (dilute ethanol). There was no depression of melting point on admixture with authentic sample. Using 0.005 or 0.01 mole of amine, a mixture of blue and gray crystals was obtained, suggesting hydrolysis and, certainly, the absence of amine exchange.

Reaction of Ethylenediamine in Absence of Copper Ion. Using 0.015 mole of ethylenediamine and omitting copper ion, only 4-iminopentane-2-one was obtained after removal of solvent under reduced pressure [0.4 gram (40%) white crystals, b.p. 80–82° 2 mm.].

Reaction with 1,3-Propanediamine. A gray solid that formed initially dissolved on continued refluxing. After 2.5 hours, the mixture was diluted with water, and gray needles of bis(4-iminopethane-2-ono copper(II) were obtained [0.3 gram, m.p. 198° dec.]. When the mixture was refluxed for a 4-hour period, the desired product was obtained only as an impurity.

Reaction with 1,2-Propanediamine. Following the general procedure only copper acetylacetonate was obtained. Using a large excess of the diamine, a trace of the desired product was obtained.

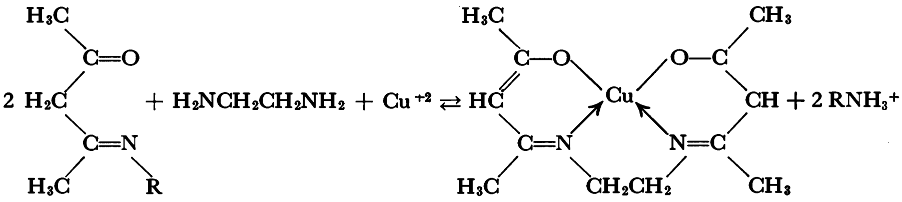
Reaction of 4-Phenyliminopentane-2-one and Ethylenediamine. Red platelets (3.0 gram, 21%) of bisacetylacetoneethylenediiminocopper(II) (m.p. 137–38°) were obtained.

Acid Dissociation Constants and Formation Constants. Attempts to determine acid dissociation constants of bisacetylacetoneethylenediimine and bisacetylacetone-*m*-phenylenediamine in 50 volume % dioxane-water were unsuccessful. The procedure used was successful when applied to bis(β-diketones) (*11*). Likewise, attempts to determine formation constants of the tetradentate β-ketoimines were unsuccessful, apparently because of hydrolysis.

The acid dissociation constant, pK_D, was determined for 4-methyliminopentane-2-one as a function of mole fraction dioxane and the data conform (within 0.03) to the expression, $pK_D = 10.78 + 14.19\ N_2$, in the range $N_2{=}0.08$ to 0.173. The half-neutralized ligand was stable in 50 volume % dioxane for at least an hour. Formation constants could not be determined for the ligand; again, hydrolysis was indicated.

Discussion

The failure of several bis-(β-ketoimine)copper(II) chelates to react with *n*-butylamine (Table I) is a marked and interesting contrast to the apparently facile reaction of the bis-(salicylaldimine)copper(II) compounds (*13, 15, 17*). On the other hand, there are some examples of amine exchange, notably the reaction of ethylenediamine with 4-phenyliminopentane-2-one or 4-iminopentane-2-one. That this reaction requires copper ion is indicated by the observation that, if copper ion is omitted, 40 to 60% of the unreacted β-ketoimine is recovered with the rest unavailable, probably because of hydrolysis or mechanical loss. It would be tempting to suggest that the equilibrium



is favorable because of the insolubility of the metal-chelate compound, but bis-(4-iminopentane-2-ono)copper(II) is more insoluble and the 4-phenyl derivative even more so. The equilibrium could be favored by the volatility of the amine, RNH_2. While this would be a·satisfactory explanation of the reaction of the imino derivative, another explanation would be required for the reaction of the phenylimino derivative.

Table 1. Summary of Results of Amine-Exchange Reactions Involving β-Ketoimines $CH_3C(=NR)CH_2COCH_3$, and Amines, $R'NH_2$, in Presence of Copper Ion

Method[a]	*β-Ketoimine, R =*	*Amine, R' =*	*Result*
A	H	$CH_3(CH_2)_3$	No exchange observed
A	C_6H_5	$CH_3(CH_2)_3$	No exchange observed
A	CH_2	$CH_3(CH_2)_3$	No exchange observed
A	CH_3[b]	$CH_3(CH_2)_3$	No exchange observed
A	CH_3[b]	C_6H_5	No exchange observed
A	CH_3	$CH_3(CH_2)_3$	No exchange[c] observed
A	C_6H_5	$CH_3(CH_2)_3$	No exchange observed
A	2,6-$(CH_3)_2C_6H_4$	C_6H_5	No exchange observed
B	H	CH_2	Exchange, 61% yield
B	C_6H_5	CH_2	Exchange, 21% yield
B	H[b]	CH_2	No exchange observed
B	H	$(CH_2)_{3/2}$	Exchange (?)

[a] Method A. $[CH_3C(=NR)CHCOCH_3]_2Cu + 2\ R'NH_2 \rightarrow [CH_3C(=NR')CHCOCH_3]_2Cu + 2\ RNH_2$.

Method B. $2\ CH_3C(=NR)CH_2COCH_3 + 2\ R'NH_2 + Cu^{+2} \rightarrow [CH_3C(=NR')CHCOCH_3]_2Cu + 2\ NH_3$.

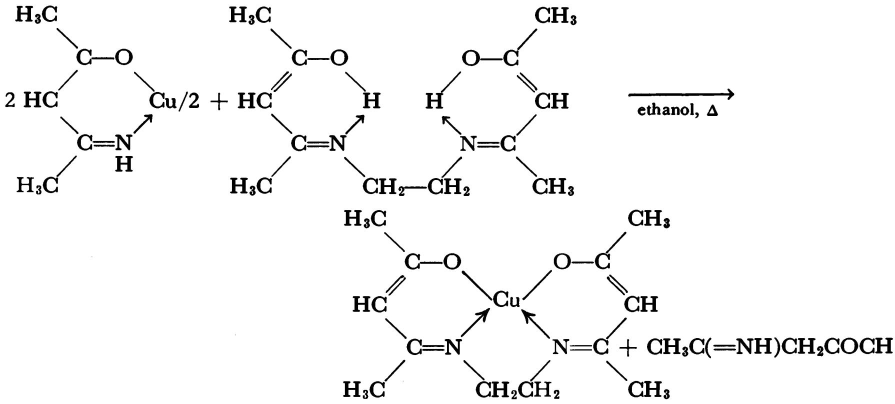
[b] Copper ion omitted.

[c] Cleavage apparently occurred.

It seems more reasonable to believe that the reaction proceeds because a ligand of greater chelating tendency is formed. This view requires the explanation of three observations: the apparent failure of the trimethylenediamine to undergo amine exchange with 4-iminopentane-2-one in the presence of copper ion; the slight tendency of propylenediamine to undergo a similar condensation; and the failure of ethylenediamine to undergo amine exchange with 4-iminopentane-2-one in the absence of copper ion.

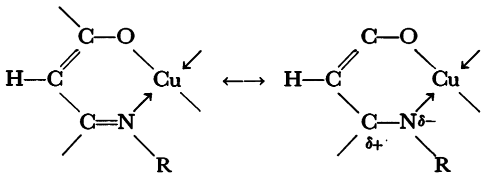
The failure of 1,3-propanediamine to undergo amine exchange is puzzling. If the amine-exchange reaction consists of a straightforward nucleophilic substitution, 1,3-propanediamine should undergo amine exchange more readily than ethylenediamine, which is a weaker base. [The log K_1 values for H^+ at 30° are 9.81 and 10.32 for ethylenediamine and 1,3-propanediamine, respectively, and the corresponding log K_2 values are 6.79 and 8.33 (2)]. On the other hand, the driving force of the reaction may be the formation of the more stable chelate species. It would be desirable to be able to compare the relative stabilities of copper chelates of the type $Cu[CH_3COCHCCH_3{=}N(CH_2)_nN{=}(CH_3)CCHCOCH_3]_2$, but formation-constant data could not be obtained in dioxane-water mixtures. The copper chelate involving a 1,3-propanediamine moiety should be less stable. [Log

K_1 for copper(II)-diamine complex is 10.36 and 9.45 for 1,2-ethanediamine and 1,3-propanediamine, respectively (*2*)]. The large difference in the stabilities of the two copper(II)-diamine complexes is attributed to an unfavorable entropy effect associated with an increase in the size of the metal-chelate ring (*2*). Extrapolating to the β-ketoimine derivatives, it seems reasonable to expect that the stability of bisacetylacetonetrimethylenediiminocopper(II) would be less than that of the ethylenediamine analog and to suspect that the former compound is less stable than bis-(4-iminopentane-2-ono)copper(II). That this is reasonable is borne out by the observation that bisacetylacetoneethylenediimine, but not bisacetylacetonetrimethylenediimine, reacts with bis-(4-iminopentane-2-ono)copper(II) (*16*).

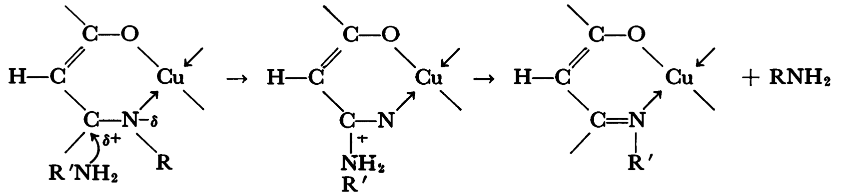


While 1,2-propanediamine (pn) does undergo amine exchange, the yield is very low. The poor yield may be due to an unfavorable equilibrium, although this would not be predicted on the basis of basicity-stability data. [The log *K* values for hydrogen ion association and first chelation process with copper ion are 9.78 and 10.58, respectively, in 0.5*M* potassium nitrate solution (*3*)]. The poor yield may be due to a greater solubility of the β-ketoimine derived from pn, since the problems of isolating pn analogs have been described (*8*). Finally, a steric factor might be involved, but further study is necessary to establish this point.

It is significant that the reaction of ethylenediamine and 4-iminopentane-2-one occurs in the presence, but not in the absence, of copper ion. One reasonable explanation of this observation is that an essential feature of the reaction is the polarization of the azomethine linkage as a result of coordination:



The electron-deficient carbon would be thus susceptible to attack by an amine molecule.

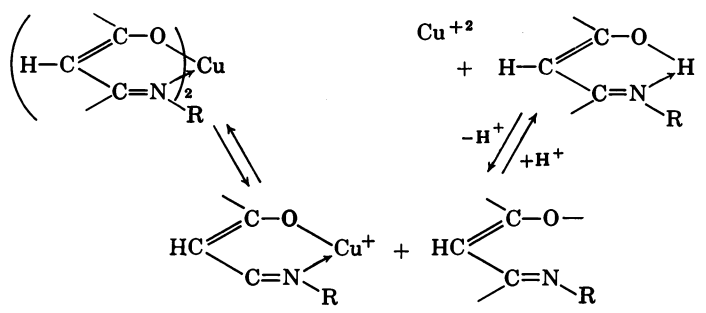


Such a mechanism has been suggested by Verter and Frost (*17*) to explain the amine-exchange reaction of butylamine and bis-(salicylaldimine)copper(II) chelates.

Another important factor, though not considered previously, is the strength of the metal-nitrogen bond. If this bond is particularly strong, the elimination of an amine is less likely; if the bond is comparatively weak, the elimination of the RN moiety becomes more likely. Thus, a nickel(II) chelate compound might be expected to undergo amine exchange more readily than the analogous copper(II) compound. In this connection, the reaction of 4-phenyliminopentane-2-one and nickel ion in ammoniacal ethanol results in bis-(4-iminopentane-2-ono)nickel(II), and it is believed that amine exchange has occurred (*14*). Such a reaction has not been observed when copper ion is substituted for nickel ion.

The Verter-Frost mechanism as presented here might suggest a common pattern of behavior for salicylaldime- and β-ketoimine–metal compounds. There are, however, some very significant differences which cast doubt upon the general validity of the proposed mechanism. The bis-(salicylaldime)copper(II) chelates undergo exchange with butylamine, though the β-ketoimine compounds fail to do so. The proposed mechanism is consistent with the failure of ethylenediamine to react with 4-iminopentane-2-one, but the mechanism, as it stands, is unable to accommodate the fact that salicylanil undergoes reaction with butylamine.

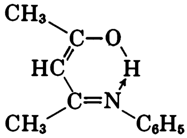
An alternative mechanism, or at least a modified one, is required. It is suggested that the reaction involves the preliminary formation of the monochelated species, as a result of either dissociation or direct formation.



Subsequently, an amine, $R'NH_2$, would react with the monochelated species in the manner suggested in the Verter-Frost mechanism. It seems likely that the driving force for the reaction would be the formation of the more stable metal-chelate compound. The equilibrium could also be shifted by loss of volatile amine—e.g., ammonia.

The plausibility of a dissociation mechanism is supported by the observation that the rate of exchange of copper ion with bis-(salicylanil)copper(II) is very great (5) and probably involves a dissociation mechanism. Moreover, the rate of exchange closely parallels stabilities of the bis-(salicylaldimine)copper(II) compounds (*5*). The same would probably be true of bis-(β-ketoimino)-copper(II) compounds and, though the copper-exchange rates apparently have never been determined for these compounds, the rate of copper ion exchange with bis-acetylacetoneethylenediiminocopper(II) is negligible (*5*). This metal-chelate compound apparently does not undergo exchange with butylamine. Thus, a reasonable explanation is that the failure of bis-(β-ketoimine)copper(II) compounds to undergo amine exchange is due to a failure to dissociate; certainly the solution stabilities of these compounds are great (*12*).

A troublesome aspect still to be considered is the observation that salicylanil undergoes amine exchange, though 4-phenyliminopentane-2-one does not. Probably, this is due to the difference in resonance stabilization of the two compounds



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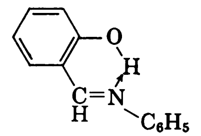
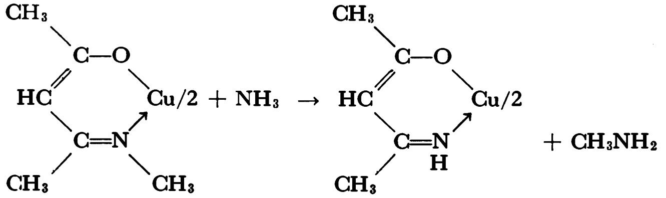


Presumably, the lack of cross resonance would cause the second structure to be the less stable. Moreover, the presence of an electron-withdrawing aromatic nucleus in the salicyl moiety decreases the electron density about the methine group.

There are several instances in which it appears that ammonia is involved in amine-exchange. Thus, the failures to prepare bis-(4-methyliminopentane-2-ono)-copper(II) might be attributed to amine exchange:



Also, the failure to prepare the copper chelates of bisacetylacetonetrimethylenediimine and 4-butyliminopentane-2-one might be attributed to amine exchange, for a similar reason. The conclusion that amine exchange has occurred is reasonable, but there are reasons for doubting that this is the only explanation.

First of all, bis-(4-iminopentane-2-ono)copper(II) was isolated when a mixture of acetylacetone, excess *N*,*N*-dimethyl-1,3-propanediamine, and copper acetate was heated, using the procedure of Charles (*4*), which has successfully been used for the preparation of bis-(salicylaldimine)copper(II) compounds. In this experiment, ammonia was not present. Secondly, the 4-imino derivative was also obtained when a compound believed to be bis-(4-methyliminopentane-2-ono)copper(II) was heated in butylamine, then diluted with water.

Thus, it appears that while amine exchange involving ammonia may be reasonable, in two instances nitrogen-alkyl cleavage has clearly occurred. Possibly, this cleavage is base-catalyzed. While 4-methyliminopentane-2-one is stable in basic solution, it is easily possible that, as a result of coordination, the *N*-alkyl bond would be more susceptible to base attack. The nitrogen-carbon cleavage may be due to air oxidation, a reaction which was postulated by Pfeiffer and coworkers (*15*) to explain nitrogen-carbon cleavage of some substituted salicylaldimine nickel(II) and copper(II) compounds.

There is some question as to whether amine exchange has occurred in the attempted preparation of bisacetylacetonetrimethylenediiminocopper(II). Bis-(4-iminopentane-2-ono)copper(II) would result from either a cleavage or an amine exchange reaction. One piece of evidence that can be brought to bear on the problem is the observation that, when methylamine is used instead of ammonia, the desired product is obtained. The cleavage reaction should occur more readily in the presence of methylamine, inasmuch as a greater concentration of hydroxide ion would be present. However, only 30% of the amount of 1,3-propanediamine expected for amine exchange was obtained.

Literature Cited

(1) Anselimino, O., *Ber.* **40**, 3474 (1907).
(2) Bertsch, C. R., Fernelius, W. C., Block, B. P., *J. Phys. Chem.* **62**, 444 (1958).
(3) Carlson, G. A., McReynolds, J. P., Verhock, F. H., *J. Am. Chem. Soc.* **67**, 1334 (1945).
(4) Charles, R. G., *J. Org. Chem.* **22**, 677 (1957).
(5) Duffield, R. B., Calvin, M., *J. Am. Chem. Soc.* **68**, 557 (1946).
(6) Eichhorn, G. H., "The Chemistry of the Coordination Compounds," J. C. Bailar, Jr., ed., Chap. 21, Reinhold, New York, 1956.
(7) Holtzclaw, H. F., Jr., Collman, J. P., Alire, R. M., *J. Am. Chem. Soc.* **80**, 1100 (1958).
(8) Hovey, R. J., O'Connell, J. J., Martell, A. E., *Ibid.*, **81**, 3189 (1959).
(9) Knovenagel, E., Raushaupt, W., *Ber.* **31**, 1030 (1898).
(10) Martell, A. E., Belford, R. L., Calvin, M., *J. Inorg. Nucl. Chem.* **5**, 170 (1958).
(11) Martin, D. F., Fernelius, W. C., *J. Am. Chem. Soc.* **81**, 1509 (1959).
(12) Martin, D. F., Janusonis, G. A., Martin, B. B., *Ibid.*, **83**, 73 (1961).
(13) Muto, T., *Nippon Kagaku Zasshi* **76**, 252 (1955).
(14) Olszewski, E. J., Martin, D. F., unpublished results.
(15) Pfeiffer, P., Offermann, W., Werner, H., *J. prakt. Chem.* **159**, 313 (1941).
(16) Struss, A. W., bachelor thesis, University of Illinois, 1962.
(17) Verter, H. S., Frost, A. E., *J. Am. Chem. Soc.* **82**, 85 (1960).
(18) Vogel, A. I., "Textbook of Practical Organic Chemistry," p. 653, Longmans, Green, New York, 1956.

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Catalytic Hydrogenation by Pentacyanocobaltate(II)

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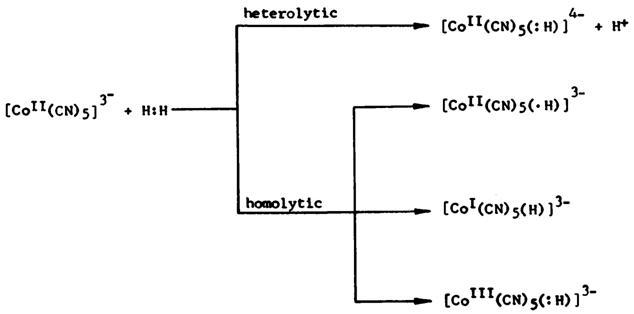
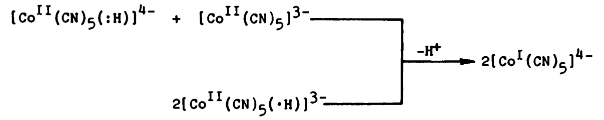
A variety of substrates have been catalytically hydrogenated at room temperature and 1-atm. hydrogen pressure by pentacyanocobaltate(II) anion. Conjugation is required for the reduction of C=C bonds. The effects of detailed molecular structure on reducibility and of cyanide-cobalt ratio on mode of reduction have been noted. Poisoning and reactivation of the catalyst as well as the effect of alkali are described, and mechanisms are tentatively proposed for these phenomena. It is concluded that the aging reaction of pentacyanocobaltate(II) is reversible. A dimerization of acrylic acids at elevated temperatures was found.

The absorption of molecular hydrogen by aqueous solutions of cyanocobaltate(II) was first reported by Iguchi in 1942 (5). Since then, several groups of workers have sought to determine the nature of the activating species and the product of its hydrogenation.

It is now generally agreed that the pentacyanocobaltate(II) anion is the active species involved. Cleavage of molecular hydrogen may be represented as occurring either heterolytically or homolytically, the three homolytic products shown here differing only in the position of the electron originally associated with the hydrogen atom. Each of these formulations has been considered by various workers.

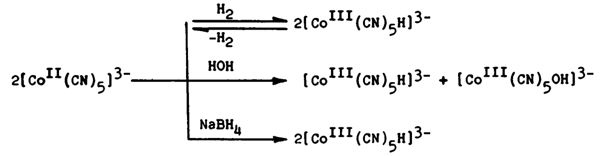


Mills, Weller, and Wheeler suggested (*12*) that the final product obtained via either heterolytic or homolytic cleavage of hydrogen was the pentacyanocobaltate(I) anion. They observed that cyanocobaltate(II) solutions lost a portion of their ability to absorb hydrogen when allowed to stand, and termed this phenomenon "aging." In addition, they found that the paramagnetism exhibited by such solutions decreased in a similar manner on standing, and inferred that this aging process was due to dimerization of the cobalt(II) species.



Griffith and Wilkinson, in a nuclear magnetic resonance study (*3*), found that a hydrido complex was formed in quantitative yield on treatment of cyanocobaltate(II) solution with sodium borohydride. A hydrido complex was also present to the extent of 3% in a solution which had not been so treated. Furthermore, saturation of the solution with hydrogen, or aging, did not increase the amount of hydrido species, and it was suggested that these latter processes involved the formation of a nonhydridic cobalt(I) species.

King and Winfield, on the other hand, after careful examination of visible and ultraviolet spectra (*9*), concluded that cyanocobaltate(II) reacts reversibly with hydrogen to form the hydrido complex. They showed further that the aging process involved the homolytic cleavage of water by cyanocobaltate(II) to yield the same hydrido complex, as well as the corresponding hydroxo complex. These same conclusions were made earlier by de Vries (*2*) in a kinetic study. Sodium borohydride also yielded this hydride, which was described as giving a simple spectrum with a characteristic absorption band at 305 mμ.



Since our initial communication (*10*) concerning the catalytic reduction of organic substrates by this homogeneous hydrogenation system, two further reports have come to our attention: de Vries (*2*) demonstrated the reduction of sorbic acid to 2-hexenoic acid and Kang (*8*) described the reductive amination of α-keto acids.

This paper discusses substrates readily reduced when added to the catalyst system in excess; and substrates reduced only when added in amounts less than that of the active catalyst present. Although the catalyst solution itself is highly alkaline, in some instances comparatively large quantities of alkali had to be added, in order for catalytic reduction to proceed.

The reactions discussed were carried out in aqueous solution, a cobalt concentration of 0.15*M*, a cyanide-cobalt ratio of 5.1, and 1 atm. of hydrogen pressure at room temperature, except where otherwise noted. Operating procedure involved the addition of potassium cyanide solution to a vigorously stirred solution of cobalt chloride in a hydrogen atmosphere. Approximately 0.7 atom of hydrogen per cobalt atom present was rapidly absorbed. The substrate was then injected and hydrogen absorption recorded.

Experimental

General Procedure. The apparatus consisted of a 500-ml. three-necked flat-bottomed Morton flask equipped with a Teflon-coated rod magnet driven by a Mag-Mix stirrer, a 125-ml. addition funnel with equilibrator, a serum cap for injection of the substrate, and a 250-ml. gas buret with leveling bulb. Aqueous potassium cyanide (100 ml., 1.53*M*) was added to the funnel and aqueous cobalt chloride (100 ml., 0.30*M*) to the flask; stirring was started, and the system was evacuated and flushed with hydrogen, and finally filled with hydrogen (1-atm. pressure). The cyanide solution then was added rapidly to the cobaltous salt solution and hydrogen absorption (approximately 260 ml.) noted. Where alkali was used, it was usually added to the cobaltous salt solution before complex formation, after which hydrogen absorption was observed to be somewhat greater (approximately 300 ml.).

After hydrogen absorption was complete, substrate was injected; liquid substrates were added as such, while solids were added in aqueous or benzene solution or suspension; acids were added as their alkali metal salts.

Formation of $[Co(CN)_5(C_4H_7)]^{-3}$. Cyanocobaltate(II) was formed in a hydrogen atmosphere, 200 ml. of solution (0.15*M* cobalt, CN/Co = 6.0) absorbing 262 ml. of H_2. In a separate flask, cyanocobaltate(II) was formed in a butadiene atmosphere, 100 ml. of solution (0.15*M* cobalt, CN/Co = 6.0) absorbing 169 ml. of butadiene. The hydrogen-saturated solution was then injected into the butadiene-saturated solution in 20-ml. increments, each containing 26.2 ml. of absorbed H_2. A total of eight injections resulted in an average absorption of 56 ml. of butadiene per injection (varied from 50 to 65 ml.).

Interaction of $[Co(CN)_5H]^{-3}$ with $[Co(CN)_5(C_4H_7)]^{-3}$. Cyanocobaltate(II) was formed in a hydrogen atmosphere, 200 ml. of solution (0.15*M* cobalt, CN/Co = 6.0) absorbing 254 ml. of H_2. In a separate flask, cyanocobaltate(II) was formed in a butadiene atmosphere, 100 ml. of solution (0.15*M* cobalt, CN/Co = 6.0) absorbing 250 ml. of butadiene. The latter solution was then transferred to a nitrogen atmosphere and the hydrogenated solution then injected into it as follows:

CoH Injected, Ml.	*Gas Desorbed, Ml.*
10	32
20	67

Vapor phase chromatographic analysis of the desorbed gas showed the presence of butene isomers in the relative ratio discussed in the text.

Reduction with Deuterium. Cyanocobaltate(II) (42.6 ml. of solution, 0.15*M* cobalt, CN/Co = 5.1) was formed in an atmosphere containing equimolar quantities of deuterium and butadiene and stirred for 15 minutes, at which time a sample of the atmosphere was taken for analysis. *trans*-2-Butene (26%), *cis*-2-butene (0.51%), and 1-butene (4.1%) as well as unreacted butadiene (53%) were separated by vapor phase chromatography and each fraction was submitted for mass spectrographic analysis. The presence of di-, mono-, and nondeuterated species was detected in each butene fraction, while the butadiene was shown to contain small quantities of mono- and dideutero species.

Reduction of H_2O_2. Cyanocobaltate(II) was formed in a hydrogen atmosphere, 200 ml. of solution (0.15*M* cobalt, CN/Co = 5.1, 0.45M KOH) absorbing 272 ml. of H_2. A solution of 30% hydrogen peroxide (Fisher reagent) was injected incrementally and hydrogen absorption noted as follows:

H_2O_2, *Mole*	H_2 *Absorbed, Ml.*
0.005	128
0.020	492
0.022	552
0.024	0

Addition of 0.003 mole of $CoCl_2$ followed by 0.0153 mole of KCN now resulted in the further absorption of 622 ml. of hydrogen (see Figure 1).

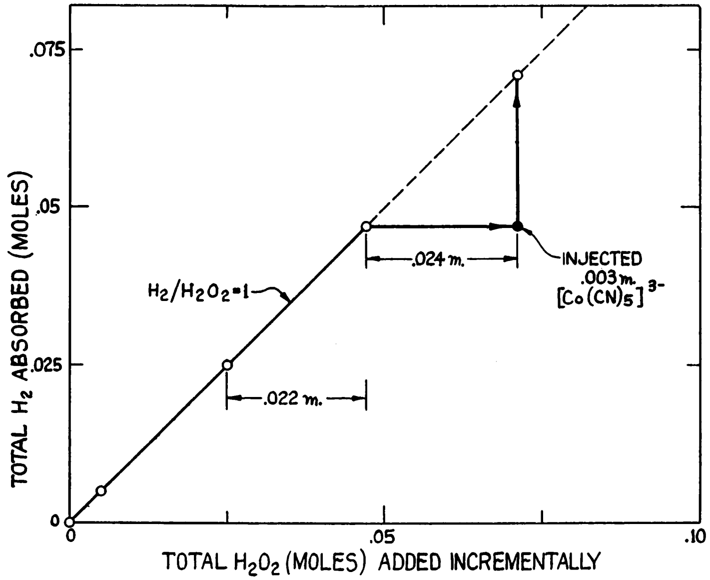


Figure 1. Hydrogenation of H_2O_2

Reduction of $K_3Fe(CN)_6$. An aqueous solution of potassium ferricyanide was injected into a cyanocobaltate(II) solution similar to that described in the previous example but containing NaOH rather than KOH and initially absorbing 323 ml. of H_2. The following hydrogen absorptions were obtained:

$K_3Fe(CN)_6$, *Mole*	H_2 *Absorbed, Ml.*
0.005	42
0.010	108
0.014	158
0.016	227
0.020	186
0.025	246
0.0275	0

Each injection was first followed by desorption of a gas assumed to be hydrogen; over-all absorption figures are reported.

Reduction of Benzoquinone. A 1*M* solution of benzoquinone in benzene was injected incrementally (5-ml. portions) into 200 ml. of prehydrogenated (312 ml. of H_2) cyanocobaltate(II) solution (0.15*M* cobalt, CN/Co = 5.1, 0.50*M* KOH). A total of 13 injections resulted in an average absorption of 97 ml. of hydrogen per injection (varied from 88 to 119 ml.).

Cyanocobaltate(II) was formed in a hydrogen atmosphere, 200 ml. of solution (0.15*M* cobalt, CN/Co = 5.1, 0.50*M* NaOH) absorbing 296 ml. of H_2. The system was saturated with benzene; then a solution of 0.05 mole of benzoquinone in 50 ml. of benzene was injected all at once; a total of 627 ml. of H_2 was absorbed in 45 minutes.

Reduction of Benzaldehyde. To a similar prehydrogenated (240 ml. of H_2) cyanocobaltate(II) solution (200 ml.) containing 0.06 mole of KOH, benzaldehyde was added incrementally in 0.01-mole portions. Five injections resulted in an average absorption of 116 ml. of hydrogen per injection; a sixth injection did not result in hydrogen absorption. Addition of a further 0.06 mole of KOH now resulted in the absorption of 159 ml. of hydrogen. The product was extracted with ether, the extract was dried over magnesium sulfate, and the residue, after filtration and evaporation, distilled to yield 4.11 grams of a fraction (b.p. 107–11°/30 mm.), identified as benzyl alcohol (1-naphthyl urethane, m.p. 134–5°; literature value for the benzyl alcohol derivative, 134°).

Addition of 100 ml. of aqueous KCN (1.53*M*) to a stirred mixture of 100 ml. of aqueous $CoCl_2$ (0.30*M*) containing NaOH (0.1 mole) and benzaldehyde (0.1 mole) in an atmosphere of hydrogen resulted in the absorption of 1052 ml. of H_2 in 90 minutes.

Reduction of Nitrobenzenes. Nitrobenzene was injected in small increments into 200 ml. of prehydrogenated (258 ml. of H_2) cyanocobaltate(II) solution (0.15*M* cobalt, CN/Co = 5.1). After an induction period of approximately 4 minutes, hydrogen absorption commenced:

Nitrobenzene, Mole	*H_2 Absorbed, Ml.*
0.01	417
0.01	357
0.01	0

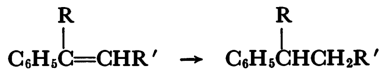
A total of seven injections of *o*-nitroanisole in 0.0082-mole increments into a similar solution containing 0.1 mole of NaOH resulted in an average absorption of 496 ml. of H_2 per injection.

Hydrogenation of Nonpoisoning Substrates

Conjugated olefins were observed to absorb one mole equivalent of hydrogen to yield mono-olefins exclusively. Although 1,4-addition predominated with butadiene and isoprene at the reaction conditions described, the mode of addition was found to change at higher cyanide-cobalt ratios as described below. 1,3-Cyclohexadiene was reduced rapidly, the rate of reduction apparently being limited only by the rate at which the catalyst itself absorbed hydrogen (60 ml. of H_2 per minute was absorbed in the presence of 0.03 mole of cobalt complex in 200 ml. of solution). Cyclopentadiene yielded cyclopentene. Mono-olefins and nonconjugated dienes were not reduced.

Styrene and its derivatives, such as α-methylstyrene, atropic acid, cinnamic acid, and cinnamyl alcohol, were readily reduced (acids were added as their salts), yielding the corresponding dihydro derivatives (Table I). However, propenylbenzene, *unsym*-diphenylethylene, and stilbene absorbed no hydrogen.

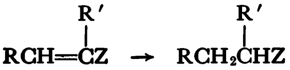
Table I. Hydrogenation of Styrenes



$$C_6H_5\overset{R}{\overset{|}{C}}{=}CHR' \rightarrow C_6H_5\overset{R}{\overset{|}{C}}HCH_2R'$$

R	*R′*	*% H_2 Absorbed*	*Initial Rate, Ml./Min.*
C_6H_5	H	0	0
COO^-	H	101	40
CH_3	H	76	7
H	H	89	21
H	CH_3	0	0
H	CH_2OH	85	7

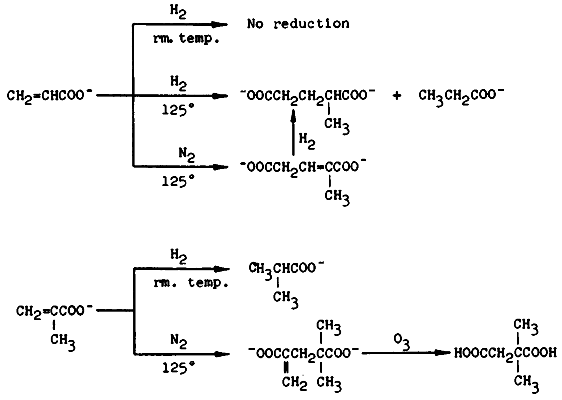
Table II. Hydrogenation of α,β-Unsaturates



$$\mathrm{RCH{=}\overset{R'}{\overset{|}{C}}Z \rightarrow RCH_2\overset{R'}{\overset{|}{C}}HZ}$$

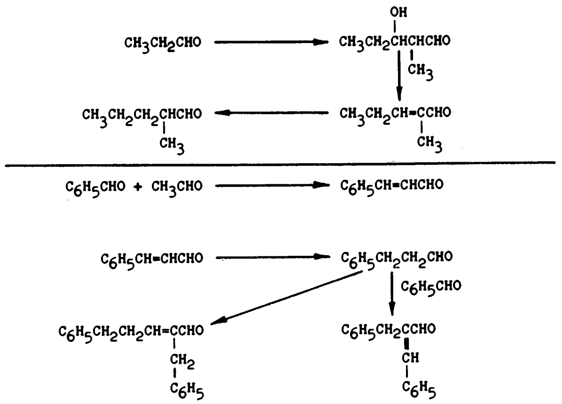
R	*R'*	*% H_2 Absorbed*		*Initial Rate, Ml./Min.*	
		Z = CHO	*Z = COO⁻*	*Z = CHO*	*Z = COO⁻*
H	C_6H_5	..	101	..	40
H	CH_2COO^-	..	81	..	10
H	CH_3	0	97	0	35
H	H	0	0	0	0
CH_3	H	11	0	3	0
CH_3	CH_3	57	0	22	0

α,β-Unsaturated aldehydes and acids were reduced, yielding the corresponding saturated derivatives (Table II). However, the parent compounds, acrolein and acrylic acid, were not. An interesting structural specificity was noted, in that methacrolein was not reduced, but methacrylic acid was quantitatively hydrogenated to yield isobutyric acid. On the other hand, crotonaldehyde was partially reduced while crotonic acid absorbed no hydrogen, and tiglic aldehyde was reduced while tiglic acid was not. The α-substituted acrylic acids, itaconic and atropic acids, were also reduced, their aldehyde counterparts not being examined.



The reduction of acrylic acid was attempted at elevated temperatures. Surprisingly, the reaction was found to yield not only propionic acid, but also the dimer, α-methylglutaric acid. When the reaction was conducted in the absence of hydrogen, the product obtained was 3-methylglutaconic acid, which apparently is the precursor of the saturated dimer formed in a hydrogen atmosphere. Similarly, methacrylic acid yielded α-methylene-γ,γ-dimethylglutaric acid when heated with cyanocobaltate(II) in the absence of hydrogen. Its structure was established via ozonolysis. Similar dimerizations have been reported for acrylic acid (*1*, *14*), methacrylate ester (*7*, *11*), crotonic acid (*13*), and its diethylamide (*15*).

A saturated aldehyde was found to absorb hydrogen to yield a dimeric aldehyde; thus, propionaldehyde formed α-methylvaleraldehyde. That this product was the result of a base-catalyzed aldol condensation was indicated by the finding that both propionaldol and its dehydration product, α-methylpentenal, yielded α-methylvaleraldehyde when hydrogenated in this catalyst system.



Mixed aldehydes yielded similar condensation products. For example, excess benzaldehyde reacted with acetaldehyde to form α-benzylcinnamaldehyde; presumably, cinnamaldehyde and phenylpropionaldehyde were intermediates. Cinnamaldehyde itself yielded α-benzylphenylpentenal.

Absorption of Butadiene by Cyanocobaltate(II). Of the various substrates reduced by this catalyst system, butadiene was especially convenient for use as a model substrate in a study of mechanism, since its absorption, as well as desorption of product butenes, could be readily followed using a gas buret, and the products formed were easily analyzed by vapor phase chromatography.

The formation of cyanocobaltate(II) solutions in a butadiene atmosphere resulted in absorption of the gas in varying quantities, depending on the cyanide-cobalt ratio employed (Figure 2). Maximal absorptions were observed at CN/Co values of 3.5 and 6.0 ($C_4H_6/Co = 0.34$ at the latter ratio), the absorptions being

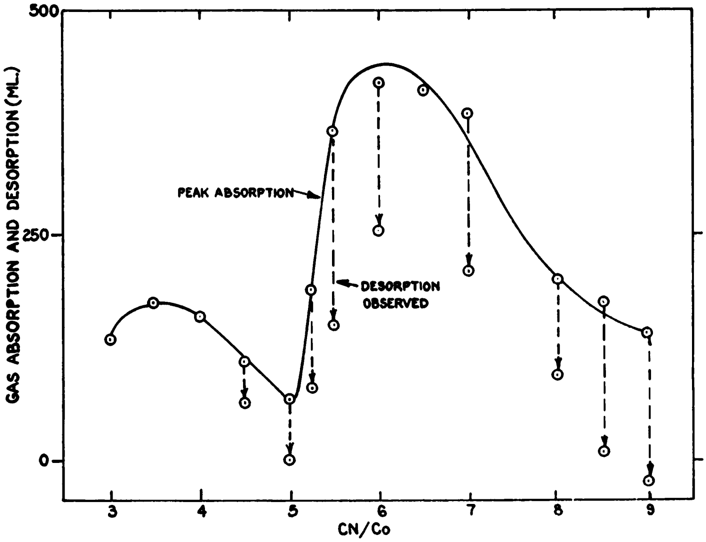


Figure 2. Butadiene absorption-desorption by 0.25M cyanocobaltate(II)

followed by slower desorptions of product butenes in the range of CN/Co values, 4.5 to 9.0. The following tabulation lists the relative ratios of butene isomers contained in the gas phase following desorption:

CN/Co	*trans-2-Butene*	*cis-2-Butene*	*1-Butene*
4.5	86	1	13
5.5	70	1	29
6.0	12	3	85
8.5	19	1	80

The change from a predominantly *trans*-2-butene product to one consisting mainly of 1-butene at ratios of 6 or higher is striking, and has also been observed by others (*16*). These reductions may be described as selective, since only monoolefin is formed and the product composition may be controlled.

Since the "aging" reaction of cyanocobaltate(II) results in the formation of hydrido complex, the question arises as to which cobalt species is involved in the absorption of butadiene. If the hydride is the reactive species, absorption would be expected to increase with time. In Figure 3 it may be seen that the absorption of butadiene by cyanocobaltate(II) does increase with time in a manner paralleling the decrease in hydrogen absorption capacity (*12*).

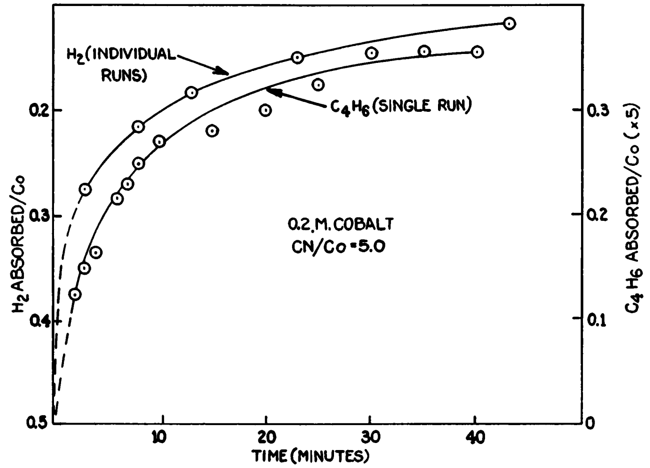


Figure 3. Effect of aging H_2 and C_4H_6 absorption

Reactions with Hydrido Complex. Upon injection of a prehydrogenated cyanocobaltate(II) solution (0.15*M* cobalt, CN/Co = 6.0) into an atmosphere of butadiene, the gas was rapidly absorbed, 0.92 mole of butadiene being taken up for each hydrogen atom previously absorbed. Similarly, when the injection was made into a butadiene-saturated cyanocobaltate(II) solution in a butadiene atmosphere, 1.08 moles of butadiene were absorbed. These results provide evidence of the addition of butadiene to the hydrido complex in the following manner:

$$[Co(CN)_5H]^{-3} + C_4H_6 \rightarrow [Co(CN)_5(C_4H_7)]^{-3} \quad (1)$$

Similar additions of transition metal hydrocarbonyls to conjugated dienes have been described, there being a close parallel in the addition of cobalt hydrocarbonyl to butadiene (*6*).

Hydrolysis may explain the formation of butenes from butadiene in the absence of a hydrogen atmosphere:

$$[Co(CN)_5(C_4H_7)]^{-3} + H_2O \rightarrow [Co(CN)_5OH]^{-3} + C_4H_8 \quad (2)$$

However, if the addition of butadiene to hydrido complex is reversible, it is possible that the butenes were formed exclusively by interaction of butadiene and hydrido complexes (Equation 3).

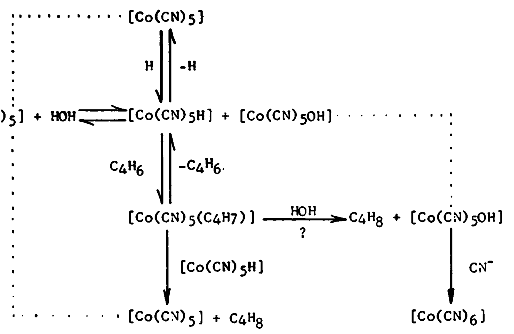
$$[Co(CN)_5(C_4H_7)]^{-3} + [Co(CN)_5H]^{-3} \rightarrow 2[Co(CN)_5]^{-3} + C_4H_8 \quad (3)$$

Upon injection of $Co(C_4H_7)$ into CoH in an atmosphere of hydrogen, desorption followed by absorption was noted, the over-all absorption being very small. [The abbreviated formulas are used to represent the complex species present in butadiene- and hydrogen-saturated cyanocobaltate(II) solutions, respectively.] No reaction occurred when $Co(C_4H_7)$ was injected into an atmosphere of hydrogen only, while addition of $Co(C_4H_7)$ to CoH or vice versa in a nitrogen atmosphere resulted in a rapid desorption of butenes (relative ratios: 82% 1-butene, 17% trans-2, 1% cis-2; 0.15*M* cobalt, CN/Co = 6.0). These experiments provide evidence for Equation 3, the pentacyanocobaltate(II) formed in the elimination of butenes now being able to absorb an equimolar quantity of hydrogen. Whether or not hydrolysis (Equation 2) is also involved in the formation of butenes under certain conditions has not been established.

Reduction with Deuterium. The absorption of an equimolar mixture of deuterium and butadiene by cyanocobaltate(II) (CN/Co = 5.1) resulted in the formation of butenes with the expected distribution of isomers (85% trans-2, 1% cis-2, 13% 1-butene), each containing di-, mono-, and nondeuterated species. The dideuterated product adds to the evidence concerning the role of the hydrido complex in the butadiene absorption and butene desorption processes. The mono- and nondeuterated products are also compatible with this evidence, since it is known that a portion of the hydrido complex is formed via the aging reaction of cyanocobaltate(II) involving the solvent water. The recovered butadiene contained small quantities of mono- (2.8%) and dideutero (0.4%) species, indicating reversibility of the reaction of hydrido complex with butadiene (Equation 1). This reversibility was considered above as an alternative explanation for the formation of butenes from butadiene in the absence of a hydrogen atmosphere, and indicates that a hydrolytic mechanism is not required. That the final step leading to butene formation was irreversible was demonstrated by mixing the pure butene isomers with cyanocobaltate(II) solutions in both the presence and absence of hydrogen. In each case, the starting isomer was recovered essentially unchanged. Authentic dideuterated butenes were obtained for mass spectrometer calibration by reacting an equimolar mixture of deuterium and butadiene with cyanocobaltate(II) dissolved in heavy water.

Proposed Mechanism for Butadiene Reduction. The above results are compatible with the reaction sequence illustrated below. In the absence of a hydrogen atmosphere, CoH, formed via the aging reaction of cyanocobaltate(II), reacts reversibly with butadiene to yield $Co(C_4H_7)$ which reacts further with CoH and/or undergoes hydrolysis to yield butenes. The over-all result is oxidation of cyanocobaltate(II) to cyanocobaltate(III) with concomitant reduction of butadiene to butenes.

In the presence of a hydrogen atmosphere, CoH is formed mainly by reaction of cyanocobaltate(II) with hydrogen, and the role of hydrolysis, if such exists in



the formation of butenes, is secondary to that of CoH-Co(C_4H_7) interaction. The over-all result is catalytic hydrogenation of butadiene.

The reaction of CoH with butadiene apparently is faster than its reaction with Co(C_4H_7), since its addition to the latter in a butadiene atmosphere resulted in the absorption of butadiene rather than butene desorption.

The striking change in product isomer ratios at CN/Co = 6 is most interesting with regard to the mechanism of reduction. Possibly two different butadiene complexes are formed: a π-allyl complex at low CN/Co values intermediate in the formation of *trans*-2-butene, and a σ-complex at high CN/Co ratios leading to the formation of 1-butene. Although this proposal is highly speculative, the double absorption peak observed in Figure 2 is of interest in this regard.

Hydrogenation of Poisoning Substrates

Hydrogen Peroxide. Some results obtained in the hydrogenation of hydrogen peroxide are illustrated graphically in Figure 1. Various quantities of the substrate were injected into CoH (H_2 atmosphere) containing added alkali (KOH, 3× cobalt concentration). When the quantity of peroxide added was the same as, or less than, the amount of CoH present [calculated from the amount of hydrogen absorbed originally by the cyanocobaltate(II)], one mole of hydrogen was absorbed per mole of substrate injected. When the quantity of peroxide added was greater than the amount of CoH present, no hydrogen was absorbed, the catalyst apparently being poisoned. Upon introduction of a small quantity of fresh cyanocobaltate(II) to this poisoned system, hydrogen was once again absorbed quantitatively—that is, one mole of hydrogen was absorbed per mole of the peroxide used to inactivate the catalyst.

Thus, the poisoned system could be reactivated by increasing the concentration of CoH to a value greater than the concentration of the poisoning substrate. We have rationalized these results in Equations 4 to 6.

$$[Co(CN)_5H]^{-3} + H_2O_2 \xrightarrow{\text{fast}} [Co(CN)_5OH]^{-3} + H_2O \quad (4)$$

$$[Co(CN)_5OH]^{-3} + [Co(CN)_5H]^{-3} \rightleftharpoons 2[Co(CN)_5]^{-3} + H_2O \quad (5)$$

$$2[Co(CN)_5]^{-3} + H_2 \rightleftharpoons 2[Co(CN)_5H]^{-3} \quad (6)$$

$$\text{Net reaction: } H_2O_2 + H_2 \rightarrow 2H_2O$$

Equation 4 indicates a rapid, irreversible formation of hydroxypentacyanocobaltate(III) and is analogous to the cleavage of hydroperoxides by lithium aluminum hydride (*17*) involving oxygen-oxygen bond scission. Equation 5 indicates formation of cyanocobaltate(II) via a reverse "aging" reaction (*2, 9*) which thus is considered to be reversible, and is the key step in the reactivation of the poisoned system. Equation 6 shows reformation of CoH (*2, 9*), the net result being reduction of hydrogen peroxide to yield water.

It is possible that a small portion of the hydroxo complex is also formed by the reaction of pentacyanocobaltate(II) with hydrogen peroxide, which is known to be almost quantitative (*4*). No cyanocobaltate(III) species is known to activate hydrogen, and we have observed that the addition of hexacyanocobaltate(III) to CoH (H_2 atmosphere) does not result in absorption of hydrogen.

Ferricyanide. The addition of less than stoichiometric amounts of potassium ferricyanide to CoH (H_2 atmosphere) resulted in hydrogen evolution. However, when this procedure was carried out with CoH containing added alkali (NaOH, 3× cobalt concentration), hydrogen evolution was followed by hydrogen absorption, 0.82 atom of hydrogen being absorbed over-all per mole of ferricyanide injected. As was observed in the hydrogenation of hydrogen peroxide, when the quantity of substrate added was less than the amount of CoH calculated to be present, hydrogen was absorbed; when the quantity added was greater, no hydrogen was absorbed, the catalyst apparently being poisoned.

These results are interpreted in Equations 7 and 8.

$$[Co(CN)_5]^{-3} + [Fe(CN)_6]^{-3} \rightarrow [(CN)_5Fe(CN)Co(CN)_5]^{-6} \qquad (7)$$

$$[(CN)_5Fe(CN)Co(CN)_5]^{-6} + OH^- \rightarrow [Fe(CN)_6]^{-4} + [Co(CN)_5OH]^{-3} \qquad (8)$$

Equation 7 shows the interaction of ferricyanide and cobaltocyanide to form a binuclear complex as described by Haim and Wilmarth (*4*). It is probable that the hydrogen evolution noted occurs via displacement of the equilibrium shown in Equation 6. Equation 8 defines the role of alkali, the presence of which is required to effect the catalytic reduction of ferricyanide. The hydroxo complex so obtained may then undergo the reverse aging process shown in Equation 5 to reform cyanocobaltate(II), which then absorbs hydrogen. The over-all result is reduction of ferri- to ferrocyanide by hydrogen.

Other inorganic salts which have been reduced by this catalyst system include potassium permanganate, dichromate, and nitrite. Reduction of the elements, oxygen, sulfur, and bromine has also been observed.

Benzoquinone. The formation of cyanocobaltate(II) in a hydrogen atmosphere and in the presence of excess benzoquinone resulted in the absorption of only 40% of that amount of hydrogen normally taken up in the formation of CoH, and the substrate was not catalytically reduced; addition of alkali did not activate the system. When excess benzoquinone was added to CoH (H_2 atmosphere), hydrogen was not absorbed and, again, alkali did not activate the system. The addition of less than stoichiometric quantities of substrate also resulted in no hydrogen absorption.

However, when small increments of substrate were added to CoH containing added alkali (KOH, 3× cobalt concentration), 1.4 atoms of hydrogen were absorbed per mole of quinone. This effect of alkali is similar to that noted in the reduction of ferricyanide. However, with benzoquinone, the addition of excess substrate to CoH containing added alkali still resulted in the absorption of hydrogen, the hydrogen atom to substrate ratio being reduced to 0.98. Furthermore, the presence of excess quinone during the formation of cyanocobaltate(II) with added alkali did not prevent catalytic reduction.

We have rationalized these results in Equations 9, 10, and 11.

$$[Co(CN)_5H]^{-3} + C_6H_4O_2 + OH^- \rightarrow [Co(CN)_5(C_6H_4O_2)]^{-4} + H_2O \qquad (9)$$

$$[Co(CN)_5(C_6H_4O_2)]^{-4} + OH^- \rightarrow [Co(CN)_5OH]^{-3} + (C_6H_4O_2)^{-2} \qquad (10)$$

$$2[Co(CN)_5]^{-3} + C_6H_4O_2 \rightarrow [(CN)_5Co(C_6H_4O_2)Co(CN)_5]^{-6} \qquad (11)$$

Equation 9 indicates the addition of benzoquinone to CoH to form a new complex which cannot react further with CoH. Equation 10 defines the role of excess alkali in effecting the catalytic reduction of benzoquinone. As shown in previous examples, the hydroxo complex may then undergo the reverse aging process, leading to hydrogen absorption. The over-all result is reduction of benzoquinone to hydroquinone when limited amounts of substrate are available, and to quinhydrone when excess substrate is available. Equation 11 is an attempt to explain the lowered amount of hydrogen absorption noted when cyanocobaltate(II) is prepared in the presence of excess benzoquinone. Displacement of reduced substrate from this binuclear complex by alkali is assumed, since quinone was catalytically reduced when the above procedure was carried out in the presence of added alkali.

The reduction of anthraquinone differed from that of benzoquinone in that small increments of the substrate were catalytically reduced (H/substrate = 2.0) even in the absence of added alkali. It would appear that the initial complex formed in this case either is spontaneously hydrolyzed or interacts with the excess CoH present.

Benzaldehyde. The addition of less than stoichiometric quantities of benzaldehyde to CoH (H_2 atmosphere) did not result in hydrogen absorption. However, when this procedure was carried out with CoH containing added alkali (KOH, 2× cobalt concentration), hydrogen was taken up, 1.0 atom of hydrogen being absorbed per mole of substrate. Since benzyl alcohol was isolated in 66% yield, it is assumed that a portion of the product may have been formed via a competitive Cannizzaro reaction. Reinforcing this assumption is the observation of an apparent depletion of alkali during the run.

As was the case with benzoquinone, the presence of excess substrate during the formation of cyanocobaltate(II) with added alkali did not prevent catalytic reduction, while addition of alkali to CoH-substrate(excess) did not activate the system.

The following equations are implied:

$$[Co(CN)_5H]^{-3} + C_6H_5CHO \rightarrow [Co(CN)_5(C_6H_5CH_2O)]^{-3} \qquad (12)$$

$$[Co(CN)_5(C_6H_5CH_2O)]^{-3} + H_2O \xrightarrow{OH^-} [Co(CN)_5OH]^{-3} + C_6H_5CH_2OH \qquad (13)$$

A similar explanation is employed as for benzoquinone, except that there is no evidence of interaction of pentacyanocobaltate(II) itself with benzaldehyde, the normal quantity of hydrogen being absorbed when the catalyst is formed in the presence of an excess of the substrate.

Nitrobenzene. Observations made on the formation of cyanocobaltate(II) in the presence of excess nitrobenzene, and on the addition of an excess of this substrate to the prehydrogenated complex, were identical to those made with benzoquinone as the substrate. However, a difference was noted when less than stoichiometric quantities of nitrobenzene were added. After a short induction period of approximately 4 minutes, hydrogen absorption commenced, 3.3 atoms of hydrogen being absorbed per mole of substrate (no absorption occurred with benzoquinone in the absence of added alkali). Further additions of small increments of the substrate resulted in the same amounts of hydrogen absorption until a total of 2.0 atoms of hydrogen had been taken up per atom of cobalt present, when absorption ceased; the system could then be reactivated by the addition of alkali. Thus, an alkali effect was found here also, but only after partial reduction of the nitrobenzene.

When small increments of nitrobenzene were added to CoH containing added alkali, 4.3 atoms of hydrogen were absorbed per mole of substrate. The reduction was catalytic, the absorption of hydrogen continuing beyond a H/Co value of 2.0. The addition of excess substrate to CoH containing added alkali resulted in the absorption of only a small quantity of hydrogen.

The hydrogen-substrate ratio of 4.3 indicates formation of azobenzene as the main product, as well as some hydrazobenzene. Both products were isolated from such a run in a 2 to 1 ratio, respectively. Addition of less than stoichiometric quantities of azobenzene to CoH (no added alkali) did not result in hydrogen absorption. However, absorption of 0.53 atom of hydrogen per mole of azobenzene was observed upon further injection of small amounts of the substrate after alkali was added; a 69% yield of hydrazobenzene was isolated.

These results have been interpreted in Equations 14, 15, and 16.

$$5[Co(CN)_5H]^{-3} + C_6H_5NO_2 \rightarrow 4[Co(CN)_5]^{-3} + 2H_2O + \text{complex X} \qquad (14)$$

$$\text{Complex X} + OH^- \rightarrow [Co(CN)_5OH]^{-3} + \text{reduction products} \qquad (15)$$

$$[Co(CN)_5]^{-3} + C_6H_5NO_2 \rightarrow \text{complex Y} \qquad (16)$$

Since it was observed that absorption ceased after 3.3 atoms of hydrogen were taken up per mole of nitrobenzene, Equation 14 is shown as producing 4 moles of cyanocobaltate(II) per mole of substrate via reaction of the latter with CoH. Since further absorption of hydrogen occurred only upon introduction of alkali, it is implied that an intermediate complex, X, is formed which is not subject to further reaction with CoH but may be decomposed by alkali. The stoichiometry of this equation requires formulation of complex X as $[Co(CN)_5(C_6H_5NH)]^{-3}$. However, since absorption ceased after two atoms of hydrogen had been absorbed per atom of cobalt present, it is implied that a binuclear complex is formed, perhaps involving phenylhydroxylamine, azobenzene, or some other reduction intermediate.

Equation 14 actually represents the result of several consecutive reactions involving additions of CoH to nitrobenzene and intermediates such as nitrosobenzene to form complexes subject to further interaction with CoH to yield reduction products in a manner similar to that postulated for the hydrogenation of butadiene (see Equations 1 and 3). Equation 15 defines the role of alkali whereby reduction products are released and the hydroxo complex so formed is able to undergo the reverse aging process as discussed in other examples. Equation 16 is similar to that shown for benzoquinone (Equation 11) and indicates a possible interaction of the substrate with nonhydrogenated cyanocobaltate(II).

Substituted nitrobenzenes gave similar results on reduction of less than stoichiometric quantities in the absence of added alkali, hydrogen atom–substrate ratios of 3.0 to 4.1 being obtained while cessation of hydrogen absorption occurred at H/Co = 2.0 in all cases. Azoxy and azo compounds were isolated from *o*-nitrotoluene (H/substrate = 3.9); *p*-nitrotoluene (H/substrate = 3.2) yielded a mixture of azoxy and hydroxylamine derivatives, the latter believed to be the immediate precursor of the bimolecular product. Reduction of *o*-nitroanisole in the presence of added alkali (NaOH, 3.3× cobalt concentration) resulted in the absorption of 5.0 atoms of hydrogen per mole of substrate, indicating complete reduction to the hydrazo compound.

Summary

The substrates reduced in this catalyst system may be classified as those which are readily reduced when added in excess, and those which must be added in less than stoichiometric amounts and/or require the presence of added alkali in order for catalytic hydrogenation to proceed.

Reduction of the first grouping of substrates, as exemplified by butadiene, appears to depend on a reversible reaction with CoH leading to the formation of an intermediate complex which may then react further with CoH to yield the reduced product; a superimposed hydrolytic mechanism cannot be ruled out at this time. In the absence of hydrogen, the substrate is reduced in a similar manner, CoH being provided via the aging reaction. The nature of the product obtained from conjugated dienes is dependent on the cyanide-cobalt ratio employed in formation of the catalyst. Small changes in molecular structure may determine reducibility or nonreducibility within a given class of substrates. A dimerization of acrylic acids has been observed in the absence of hydrogen at elevated temperatures.

Substrates in the second grouping may be subdivided into those (hydrogen peroxide, ferricyanide, and nitrobenzene) undergoing catalytic reduction only when added to the catalyst in less than stoichiometric quantities in the presence of additional alkali, and those (benzoquinone and benzaldehyde) undergoing catalytic reduction when added in excess quantities in the presence of alkali. Of all these substrates, only hydrogen peroxide has not been studied in the absence of added alkali. Ferricyanide, benzoquinone, and benzaldehyde could be reduced only when alkali was added. Nitrobenzene underwent partial reduction and anthraquinone was quantitatively reduced without requiring additional alkali.

These observations led to the following conclusions:

Initial complexes formed from the interaction of CoH and hydrogen peroxide, nitrobenzene, or anthraquinone either react further with the excess CoH present to form pentacyanocobaltate(II) or are spontaneously hydrolyzed to yield hydroxypentacyanocobaltate(III). The latter species may then undergo the reverse aging process with CoH, forming pentacyanocobaltate(II), thereby effecting catalytic hydrogenation.

With nitrobenzene, reduction to an intermediate stage results in the formation of a complex which, as is also the case with the initial complexes formed with ferricyanide, benzoquinone, and benzaldehyde, cannot react in the manner shown in the first conclusion. These species require the presence of added alkali, which apparently effects the displacement of reduced substrate by hydroxyl anion to yield hydroxypentacyanocobaltate(III). All of the substrates mentioned have been found to undergo catalytic hydrogenation when added to the catalyst system in less than stoichiometric quantities in the presence of alkali.

The addition of excess quantities of hydrogen peroxide, ferricyanide, or nitrobenzene to the catalyst in the presence of added alkali did not result in catalytic reduction, implying that the reverse aging reaction was not the fastest reaction involved; similar additions of benzoquinone or benzaldehyde resulted in catalytic reduction, implying that the reverse aging reaction in these cases was the fastest.

The key step involved in reactivation of a poisoned catalyst is considered to be the reverse aging process.

Since the pentacyanocobaltate(II) system is simply prepared and hydrogenations are rapid, we now have an additional hydrogenation method suitable for use in the laboratory. The mechanisms proposed may be helpful in understanding poisoning and activation processes as well as selectivities observed in heterogeneous or biological catalyst systems.

Acknowledgment

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Literature Cited

(1) Bergmann, E., *et al.*, *Ber.* **64**, 1493 (1931).
(2) de Vries, B., *Koninkl. Ned. Akad. Wetenschap., Proc., Sect. B* **63**, 443 (1960).
(3) Griffith, W. P., Wilkinson, G., *J. Chem. Soc.*, **1959**, 2757.
(4) Haim, Albert, Wilmarth, W. K., *J. Am. Chem. Soc.* **83**, 509 (1961).
(5) Iguchi, M., *J. Chem. Soc. Japan* **63**, 634 (1942).
(6) Jonassen, H. B., Stearns, R. I., Kenttämaa, J., Moore, D. W., Whittaker, A. G., *J. Am. Chem Soc.* **80**, 2586 (1958).
(7) Kealy, T. J., Benson, R. E., *J. Org. Chem.* **26**, 3126 (1961).
(8) Kang, J.-W., Osaka University, private communication.
(9) King, N. K., Winfield, M. E., *J. Am. Chem. Soc.* **83**, 3366 (1961).
(10) Kwiatek, J., Mador, I. L., Seyler, J. K., *Ibid.*, **84**, 304 (1962).
(11) McElvain, S. M., Aldridge, C. L., *Ibid.*, **75**, 3987 (1953).
(12) Mills, G. A., Weller, S., Wheeler, A., *J. Phys. Chem.* **63**, 403 (1959).
(13) Pechmann, H. v., *Ber.* **33**, 3323 (1900).
(14) Pechmann, H. v., Röhm, O., *Ibid.*, **34**, 427 (1901).
(15) Snyder, H. R., Putnam, R. E., *J. Am. Chem. Soc.* **76**, 33 (1954).
(16) Spencer, M. S., Dowden, D. A., (1959), (to Imperial Chemical Industries), U. S. Patent **3,009,969**, German Patent **1,114,183.**
(17) Sutton, D. A., *Chem. & Ind.* (*London*), **1951**, 272.

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16

Iron-Catalyzed Autoxidation of Mercaptoacetate

Facilitation of a Two-Electron Transfer through Coordination

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From a study of the effects of several variables on the yields of iron(III) in the oxidation of ferrous mercaptoacetate solutions, by either oxygen or hydrogen peroxide, it is concluded that a free radical reaction is involved. At relatively high concentrations of iron(II) and mercaptoacetate the results are explained by the reactions: Fe(II) + O_2 → Fe(III) + HO_2·, HO_2· + RSH$^-$ → H_2O_2 + RS·, Fe(II) + H_2O_2 → Fe(III) + HO·, HO· + RSH$^-$ → H_2O + RS·, and 2RS· → RSSR. In intermediate concentration ranges, the reactions HO_2·(HO·) (RS·) + Fe(III)(OH)(RS$_2^{-2}$ → Fe(II) + RSSR + H_2O_2(H_2O)(RS$^-$) become important. Oxygen also reacts with Fe(III)(OH)(RS)$_2^{-}{}_2$ to produce ferrous iron, and thus, appears to react with the ferric complex in a manner analogous to that of the radicals.

The metal ion–catalyzed autoxidation of thiols has been a subject of interest, especially to biochemists, since Claesson's discovery (*1*) that small amounts of iron greatly accelerated the rate by which mercaptoacetic acid was oxidized by air. It has been shown (*2, 4*) that mercaptoacetic acid is almost quantitatively oxidized to the disulfide in this reaction.

Both iron(II) and iron(III) form complexes with mercaptoacetic acid, $SRSH_2$ (*5, 11*). The ferrous complexes, Fe(II)$(RS)_2^{-2}$ and Fe(II)(OH)(RS)$^-$, are highly air-sensitive and are rapidly oxidized to the intense red ferric complex, Fe(III)OH$(RS)_2^{-2}$ (*5*). Under air-free conditions the color of this latter complex is observed to fade at moderate to fast rates because of a redox reaction in which the iron is reduced to the ferrous state and the mercaptoacetate is oxidized to the disulfide. Michaelis and Schubert (*9*) proposed that the catalysis takes place through the alternate oxidation and reduction of iron ions in a sequence similar to that just described, but Lamfrom and Nielsen (*4*) were able to show that under mildly acid conditions the rate of oxygen uptake of solutions containing iron and

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mercaptoacetate is 40 to 100 times faster than the rate of bleaching of the iron(III) complex established (*7*) under air-free conditions. The latter workers also found an enhanced bleaching rate in the presence of oxygen and proposed that a free radical mechanism is involved with the tentatively suggested steps:

$$\mathrm{Fe(II)(RS)_{complex}} + \mathrm{O_2(H_2O_2)} \longrightarrow \mathrm{Fe(III)(RS)_{complex}} + \mathrm{O_2\cdot^{-}(HO\cdot)}$$

$$\mathrm{O_2\cdot^{-}(HO\cdot)} + \mathrm{RSH^{-}} \longrightarrow \mathrm{H_2O_2\,(H_2O)} + \mathrm{RS\cdot^{-}}$$

$$\mathrm{RS\cdot^{-}} + \mathrm{Fe(III)RS)_{complex}} \longrightarrow \mathrm{Fe(II)RS_{complex}} + \mathrm{RSSR^{-2}}$$

We undertook the study of this reaction, employing conditions where limited amounts of oxygen (or hydrogen peroxide) were allowed to react with mercaptoacetate in the presence of iron ions. The amount of $\mathrm{Fe(III)(OH)(RS)_2^{-2}}$ produced was determined spectrophotometrically. Since the rate of bleaching of this complex was fast under some of the conditions, a rapid-mixing device was employed. This consisted of a spring-actuated syringe, patterned after one described by Stern and Du Bois (*12*), which injected one of the reaction mixtures into the other contained in a spectrophotometer cell.

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Experimental

Air-free ferrous mercaptoacetate solutions were prepared essentially as previously described (*5*), using redistilled mercaptoacetic acid in the appropriate buffer. The buffers consisted of mixtures of either trishydroxymethylaminomethane and its hydrochloride or of ammonia and its hydrochloride. For most of the experiments the hydrochloride concentration was 0.50*M*.

In a typical experiment either an air-saturated buffer or known volumes of an air-saturated and air-free buffer were added with syringes to a cylindrical 1.00-cm.-path-length optical cell which had been flushed with nitrogen. The mouth of the cell had been previously provided with a Teflon cap containing a small hole large enough to pass the syringe needles but with just enough tolerance to permit the escape of gases and liquids. The cell was filled to a volume of 3.15 ml. This volume filled the cell so that the meniscus was contained in the cap, providing a seal against air which was sufficient for the length of time of the experiments. The cell was immediately placed in the cell compartment of a Cary 14 spectrophotometer and the spring-actuated syringe which contained the ferrous mercaptoacetate solution was put into position. The cover of the spectrophotometer had been modified so the syringe passed through it. The syringe was held tightly in place by a collar with a set-screw. The height of the syringe had previously been adjusted so the needle came close to the bottom of the optical cell. This was necessary for maximum turbulence and most efficient mixing. On triggering the syringe, a volume of solution which calibration showed to be 0.231 ±0.002 ml. was injected into the cell. The same volume of buffer was injected into the upper part of the cap which had been hollowed out. Separate tests with dyes showed that the ejected solution did not contain a detectable amount of the injected solution (*13*). The volume of this unreacted solution was taken into account in calculating the yields.

In most experiments the absorbance at 537 mμ was followed as a function of time, using the pen-recorder of the spectrophotometer and the absorbance at zero time (the time of mixing) was determined by extrapolation. The amount of Fe(III) produced was calculated from the zero time absorbance after correcting for a blank using $3.92 \times 10^{+3}$ liter mole^{-1} cm.$^{-1}$ for the extinction coefficient. The blank was determined before each series of runs by injecting mercaptoacetate solution into the air-free buffer. The blank results from the color of the ferrous complex itself, the presence of traces of ferric iron in the injected solution, and slight traces of oxygen diffusing into the cell. The blanks were usually small, a typical value being 0.075 absorbance unit.

Oscilloscopic observations were made to estimate the mixing and reaction times. Tests with dyes showed that the mixing time was well within the 33-msec. chopping time of the spectrophotometer. Brief observations during the approximately 8-msec. view of the sample beam permitted each cycle allowed an estimate of 15 to 20 msec. for the mixing time. Similar observations with ferrous mercaptoacetate solutions injected into oxygen-containing buffers showed no differences from the tests with dyes. Apparently the oxidation is completed within a few milliseconds or less.

One series of experiments was run at pH 8.2 to determine the effect of oxygen on solutions of the ferric complex. Because of the rapid second-order rate of bleaching at this pH it was necessary to prepare a fresh stock solution of the ferric complex for each point and to work as rapidly as possible. Even so, blanks under similar conditions but in the absence of oxygen showed that in some of the experiments [high iron(III), low mercaptoacetate] appreciable production of iron(II) had occurred by the time of mixing. In spite of this, these experiments provided useful data.

Results and Discussion

pH 7.5 to 8.2. The results are reported in terms of the yield of ferric iron, which is given as the molar ratio of iron(III) produced to the amount of oxygen initially present. In Figure 1 the yield at pH 8.2 is illustrated for varying con-

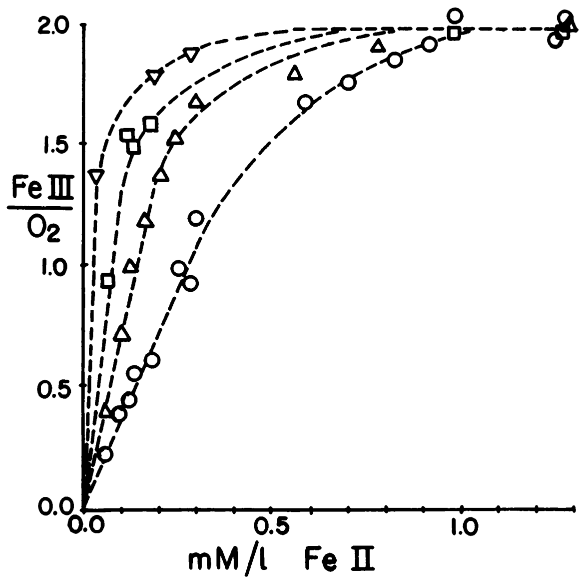

Figure 1. Ratio of iron(III) produced to initial oxygen as a function of concentrations of iron(II) and oxygen at pH 8.2

Concentration of total mercaptoacetate, 4.8 mmoles per liter

Oxygen, mmole per liter

○	*0.16*	□	*0.04*
△	*0.08*	▽	*0.02*

centrations of oxygen and iron(II) at a constant level of mercaptoacetate and in Figure 2 for a constant initial level of oxygen with varying iron(II) and mercaptoacetate concentrations. The striking feature of these diagrams is the limiting yield at high iron(II) levels of 2.0 moles of iron(III) ions per mole of oxygen. The solid lines in Figure 2 indicate the theoretical yields if this stoichiometry remains constant. In the region to the left of the intersection of the two straight lines the iron(II) concentration is limiting and oxygen is in excess. The observed yields in this region fall below the line, indicating that the stoichiometry does not remain constant but is variable. Even at the lowest concentration of iron(II) not all of the iron(II) is oxidized and ample is still available for oxidation at the end of the reaction. An important feature of the curves in this region of low yields is the increase in the ratio at a given iron(II) concentration produced by either an increase in the mercaptoacetate concentration or a decrease in the oxygen concentration. Nearly identical results were observed for repeats of some of these experiments at pH 7.5.

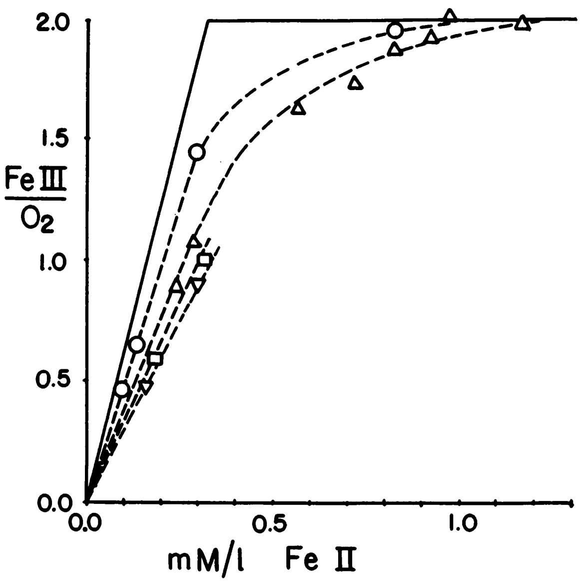

Figure 2. Ratio of iron(III) produced to initial oxygen as a function of concentrations of ferrous iron and mercaptoacetate at pH 8.2

Concentration of oxygen, 0.16 mmole per liter

Total mercaptoacetate, mmoles per liter

○	10.5	□	2.6
△	5.2	▽	1.3

Studies, also at pH 8.2, were conducted using dilute hydrogen peroxide solutions as the oxidant in place of oxygen (Figure 3). At the lowest concentration of hydrogen peroxide studied a limiting yield of 1.0 mole of iron(III) per mole of oxidant is observed. At higher concentrations the yield is seen to fall off drastically and seems to approach limiting values of less than 1.0. This appears to be due to the rapid liberation of a gas on mixing. Oscilloscopic studies showed that gas evolution was initiated and practically completed within the mixing time (*13*).

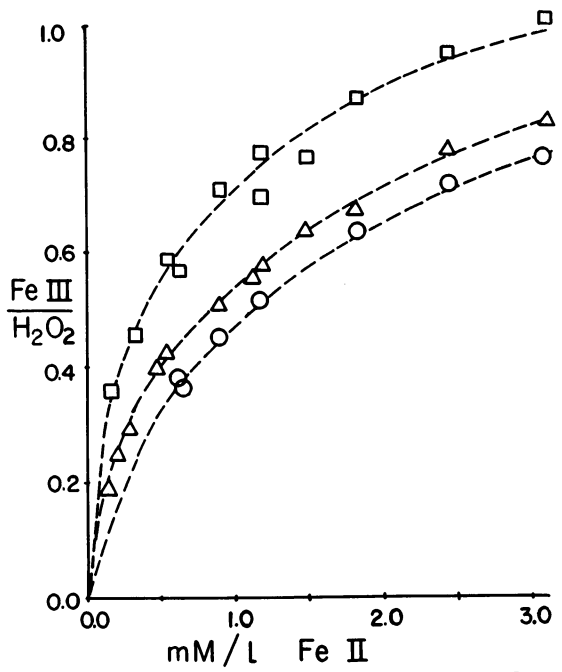

Figure 3. Ratio of iron(III) produced to initial oxygen as a function of concentrations of ferrous iron and hydrogen peroxide at pH 8.2

Concentration of total mercaptoacetate, 10.8 mmoles per liter

Hydrogen peroxide, mmole per liter

○ *0.60*	□ *0.19*
△ *0.44*	

The released gas, which presumably was oxygen, escaped from the solution and was not available for reaction; thus, the low yields.

To trap reactive intermediates in the oxidations with oxygen, experiments were performed using solutions either 0.10*M* in phenol or 0.10*M* in sodium benzoate. The results are given in Table I together with the results from similar experiments run in the absence of the added reagents. The scavenger in all but two cases studied increases the yield of iron(III). Only a small effect is observed at low iron(II) concentrations, but at high concentrations the yield is raised to the range of the limiting values, 2.0 to 2.1. The effect of sodium benzoate is also observed to be somewhat less than that of phenol (Table I).

The results of the experiments in which solutions of $Fe(III)(OH)(RS)_2^{-2}$ were injected into air-saturated buffers are presented in Table II, with results of duplicate runs with air-free buffers. The figures in the fifth column show the values of absorbance expected in the mixed solutions if no bleaching had occurred in the stock $Fe(III)(OH)(RS)_2^{-2}$ solution prior to mixing. Comparison of these absorbances with the extrapolated zero time values in the air-free blanks gives a measure of the relative amounts of ferrous and ferric iron present at the time of mixing (Table II).

In experiments where the initial concentrations of iron(II) are indicated to be relatively low, it is significant that lower zero time absorbance values are ob-

Table I. Effect of Added Phenol and Sodium Benzoate on Oxidation of Ferrous Mercaptoacetate with Molecular Oxygen

(pH 8.2, trishydroxymethylaminomethane buffer)

Initial Concn., Mmoles/Liter			*$Fe(III)/O_2$*		
Fe(II)	*Total RSH*	*O_2*	*With reagent*	*Without reagent*	*% Change in Ratio*
		0.1*M* Phenol			
0.140	1.30	0.15	0.47	0.46	+2.2
0.140	1.30	0.073	0.93	0.89	+4.5
0.140	2.61	0.15	0.54	0.54	0.0
0.140	2.61	0.073	1.11	1.08	+2.7
0.140	5.24	0.15	0.64	0.63	+1.6
0.140	5.24	0.073	1.24	1.21	+2.5
0.140	1.04	0.15	0.72	0.70	+2.8
0.140	1.04	0.073	1.42	1.37	+3.6
0.568	5.24	0.15	1.89	1.65	+14.5
0.568	5.24	0.073	2.14	1.77	+20.9
0.705	5.24	0.15	2.01	1.71	+17.5
0.870	5.24	0.15	2.06	1.87	+10.2
1.37	5.24	0.15	2.09	1.94	+7.7
		0.1*M* Sodium Benzoate			
0.095	4.95	0.15	0.44	0.44	0.0
0.889	4.95	0.15	1.92	1.87	+2.7
1.37	5.24	0.15	2.03	1.94	+4.6

Table II. Effect of Fe(III) on Oxidation of Mercaptoacetate

(pH 8.2, trishydroxymethylaminomethane buffer)

Initial Concn., Mmoles/Liter			*Absorbance, t = 0, 537 Mμ*	
Fe(III)	*Uncomplexed RSH^-*	*O_2*	*Obsd.*	*Calcd.*[a]
0.120	6.75	...	0.49	0.47
0.120	6.75	0.169	0.37	0.47
0.249	6.74	...	0.90	0.98
0.249	6.74	0.169	0.69	0.98
0.497	6.74	...	1.38	1.95
0.497	6.74	0.169	1.18	1.95
0.120	2.05	...	0.25	0.47
0.120	2.05	0.169	0.40	0.47
0.118	1.04	...	0.29	0.46
0.118	1.04	0.169	[b]	0.46
0.430	1.04	...	0.69	1.69
0.430	1.04	0.169	1.44	1.69

[a] Theoretical absorbance if no bleaching occurred.
[b] Very rapid discharge of color on mixing.

served for solutions where oxygen was initially present than in the corresponding runs where oxygen was absent (Table II). In all the runs, as soon as data could be obtained after mixing, it was observed that bleaching had commenced with the second-order kinetics characteristic of air-free iron(III)-mercaptoacetate solutions. This shows that oxygen when initially present is rapidly and completely consumed. Otherwise, the absorbances in the oxygen-containing solutions would have remained at a high initial value until the last traces of O_2 had disappeared. These experiments indicate that oxygen rapidly reacts with $Fe(III)(OH)(RS)_2^{-2}$ to produce a less highly colored complex. This latter complex is probably one of ferrous iron, since the equilibria involving the ferric species have been shown to be rapid (*4*). When about equal proportions of iron(II) and iron(III) are initially present, a net positive yield of iron(III) is observed, indicating that

$Fe(III)(OH)(RS)_2^{-2}$ does not compete as successfully for O_2 as does $Fe(II)(RS)_2^{-2}$.

The above results are consistent with the type of mechanism tentatively proposed by Lamfrom and Nielsen (*4*), but additional reactions must be included to explain all the observations. Certainly, the rapid reaction of the ferrous complexes with oxygen and hydrogen peroxide compared with the demonstrably slower reactions of mercaptoacetate with these reactants in the absence of iron salts is in agreement with Lamfrom and Nielsen mechanism. Also, the observed limiting yield of 2.0 moles of Fe(III) per mole of oxygen is consistent with their proposals. The remaining results can, at least qualitatively, be explained by assuming only a few additional steps. Several of these steps involve $Fe(III)(OH)(RS)_2^{-2}$ in what may be a general reaction of this species with one-electron oxidants.

In the Lamfrom-Nielsen scheme for each radical produced one iron(III) is obtained, and similarly one iron(III) is reduced each time a radical is reduced, giving a net zero yield of iron(III). A positive iron(III) yield implies that a radical-radical reaction takes place. This could be a reaction of the type $2RS^{-}\cdot \rightarrow RSSR^{-2}$ or may involve steps such as $HO_2\cdot + Rs\cdot^{-2} \rightarrow H_2O_2 + {}^{-}RS^{+}$ and ${}^{-}RS^{+} + RS^{-2} \rightarrow RSSR^{-2}$.

The mercaptoacetate dependence and the effects of the scavengers indicate that competition exists between $Fe(III)(OH)(RS)_2^{-2}$ and RSH^{-} for the intermediates $HO_2\cdot$ and $HO\cdot$. The reactions of these radicals result in their reduction and, also, when $Fe(III)(OH)(RS)_2^{-2}$ is involved, in the reduction of the iron to the ferrous state. The best source of electrons in this latter reaction is the ligands coordinated to the iron ion. Thus, it appears that $HO_2\cdot$ and $HO_2\cdot$ react with $Fe(III)(OH)(RS)_2^{-2}$ to give disulfide in a manner similar to that suggested by Lamfrom and Nielsen for $RS\cdot$.

In general, these free radical reactions bear some resemblance to the reactions found for the air-free bleaching of ferric mercaptoacetate (*7*) and ferric cysteinate (*6*): A bimolecular reaction occurs between two one-electron oxidants, one of which is an iron(III) ion with two mercaptide groups coordinated to it; in a two-electron reaction each of the oxidants is reduced and the mercaptides are oxidized to give a molecule of disulfide.

As is evident from the intense absorption bands characteristic of these species, charge-transfer from sulfur to the iron(III) ion readily occurs in the ferric mercaptide complexes. The iron(II) nucleus which results from such a process can in turn reduce an approaching one-electron acceptor. In this way the metal ion serves as a mediating agent in the transfer of an electron from a coordinated mercaptide ion to the oxidant. The iron(III) ion can then accept another electron from the remaining coordinated mercaptide to return to the ferrous state, while the two thiyl radicals which have been formed in close proximity combine to form a disulfide molecule. The advantages gained are (1) an increase in the reaction cross section; the radical need not directly attack the mercaptide group being oxidized but only approach the complex ion at one of a large number of points; and (2) the two thiyl radicals are formed and combined within the solvent sheath of the original ion, thus providing a low energy path for this reaction.

An analogous reaction, but one in which one ligand supplies two electrons, has been observed for the oxidation of pentammineoxalatocobalt(III) by cerium(IV). Saffir and Taube (*10*) have shown the oxalate is oxidized to carbon dioxide in a two-electron transfer, producing one equivalent of cobalt(II) and one equivalent of cerium(III).

In the steps so far discussed there is a 1 to 1 correspondence between the total number of iron(III) ions produced and the total number of radicals in solution. The fate of the iron(III) is either to remain as such when radical-radical reactions occur or to be reduced simultaneously with a radical. The lowest yield of iron(III) which is possible under these conditions is zero. Therefore, to account for the negative yields observed in Table II at least one more reaction must be proposed. The negative yields can be explained by assuming competition between +2 and +3 iron species for oxygen and/or hydrogen peroxide. Here again as the oxidant is reduced the iron in the $Fe(III)(OH)(RS)_2^{-2}$ complex is also reduced. Since only one electron is accepted by the iron, the oxygen (or hydrogen peroxide) molecule also must be reduced to a species with an odd number of electrons—i.e., be a radical—and, therefore, $Fe(III)(OH)(RS)_2^{-2}$ itself must be capable of initiating the reaction. This last reaction is indicated to be somewhat slower than initiation by the iron(II) complexes, however.

Omitting the ligands coordinated to the metal ions, the reactions which appear to be most important in the pH range 7.5 to 8.2 are:

$$\begin{aligned}
&\mathrm{Fe(II)} + \mathrm{O_2} &&\xrightarrow{k_1} \mathrm{Fe(III)} + \mathrm{HO_2}\cdot\\
&\mathrm{Fe(III)} + \mathrm{O_2} &&\xrightarrow{k_2} \mathrm{Fe(II)} + \mathrm{RSSR} + \mathrm{HO_2}\cdot\\
&\mathrm{RSH^-} + \mathrm{HO_2}\cdot &&\xrightarrow{k_3} \mathrm{RS}\cdot + \mathrm{H_2O_2}\\
&\mathrm{Fe(III)} + \mathrm{HO_2}\cdot &&\xrightarrow{k^2} \mathrm{Fe(II)} + \mathrm{RSSR} + \mathrm{H_2O_2}\\
&\mathrm{Fe(II)} + \mathrm{H_2O_2} &&\xrightarrow{k_5} \mathrm{Fe(III)} + \mathrm{HO}\cdot\\
&\mathrm{Fe(III)} + \mathrm{H_2O_2} &&\xrightarrow{k_6} \mathrm{Fe(II)} + \mathrm{RSSR} + \mathrm{HO}\cdot\\
&\mathrm{RSH^-} + \mathrm{HO}\cdot &&\xrightarrow{k_7} \mathrm{RS}\cdot + \mathrm{H_2O}\\
&\mathrm{Fe(III)} + \mathrm{HO}\cdot &&\xrightarrow{k_8} \mathrm{Fe(II)} + \mathrm{RSSR} + \mathrm{H_2O}\\
&\mathrm{Fe(III)} + \mathrm{RS}\cdot &&\xrightarrow{k_9} \mathrm{Fe(II)} + \mathrm{RSSR}\\
&2\,\mathrm{RS}\cdot &&\xrightarrow{k_{10}} \mathrm{RSSR^{-2}}
\end{aligned}$$

In addition, the liberation of gaseous oxygen in the hydrogen peroxide experiments suggests that reactions such as

$$\begin{aligned}
&\mathrm{HO}\cdot + \mathrm{H_2O_2} &&\xrightarrow{k_{11}} \mathrm{H_2O} + \mathrm{HO_2}\cdot\\
&\mathrm{HO_2}\cdot + \mathrm{H_2O_2} &&\xrightarrow{k_{12}} \mathrm{O_2} + \mathrm{HO}\cdot
\end{aligned}$$

also be included. These probably are not important when hydrogen peroxide is produced in a small steady-state concentration as in the oxygen experiments. [Further comments regarding the different behavior of hydrogen peroxide when added as a slug to a reducing solution compared to when it is produced in low steady-state concentration are given by Gordon and Taube (3).]

Effect of Higher pH

As the pH of the reaction mixture is increased, the yield increases until at pH 10.2 the limit approaches 4.0 moles of iron(III) per mole of oxygen (Figure 4);

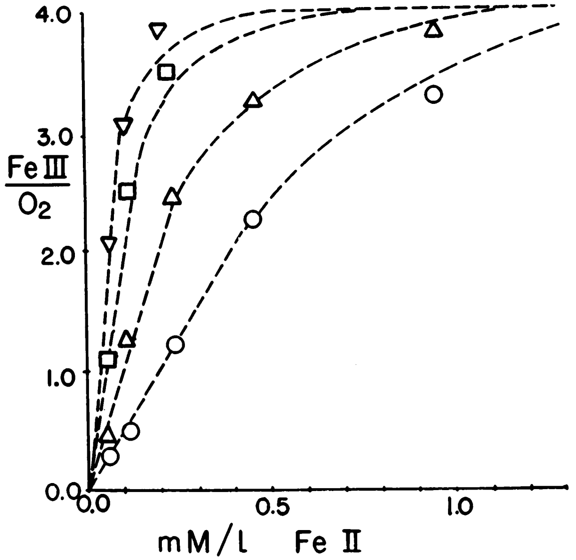

Figure 4. Ratio of iron(III) produced to initial oxygen as a function of concentrations of ferrous iron and oxygen at pH 10.2

Concentration of total mercaptoacetate, 4.8 mmoles per liter

Oxygen, mmole per liter

○	*0.14*	□	*0.04*
△	*0.07*	▽	*0.02*

this indicates that changes in the reactive species occur as the pH becomes greater than 8.2. However, only after it has been determined how the actual rates themselves are affected by pH will it be possible to ascertain the cause for the increased yield. For example, if the reactive species at low pH are actually protonated complexes, these will decrease in number as the pH increases; therefore, possibly slower oxidations of ferrous iron by $HO_2\cdot$ and $HO\cdot$ can be observed, but on the other hand, it may be found that hydroxylated ferrous complexes are more reactive regarding oxidation by $HO_2\cdot$ and $HO\cdot$ than nonhydroxylated species. In the first case, the rate of the over-all reaction would decrease, but in the second would increase as the pH increases. Another factor to be taken into account is the change in the degree of ionization of the mercaptoacetate ion ($pK_{2a} = 10.5$). This must certainly affect the participation of uncomplexed mercaptoacetate in these reactions, since at low pH the thiol is completely protonated but at high pH is appreciably ionized.

Conclusions

The results of this work indicate that the Michaelis-Schubert catalysis mechanism is actually a limiting mechanism which is approached only in solutions at a high pH and high iron(II) concentration. Under other conditions, especially in mildly alkaline and acid solutions, free radical reactions which favor oxidation of mercaptide are important. McCormick and Gorin (*8*) recently have reported on an investigation of the action of oxygen on cobalt(II)-cysteinate solutions. In qualitative agreement with the present results they found that at high pH the principal reaction involves only the oxidation of the metal ions from the +2 to the +3 state but at lower pH extensive disulfide formation also occurred.

Literature Cited

(1) Claesson, P., *Ber.* **14,** 409, 412 (1881).
(2) Eliott, K. A. C., *Biochem. J.* **24,** 310 (1930).
(3) Gordon, G., Taube, H., *Inorg. Chem.* **1,** 691 (1962).
(4) Lamfrom, H., Nielsen, S. O., *J. Am. Chem. Soc.* **79,** 1956(1957).
(5) Leussing, D. L., Kolthoff, I. M., *Ibid.,* **75,** 3904 (1953) and references cited here.
(6) Leussing, D. L., Mislan, J. P., Goll, R. J., *J. Phys. Chem.* **64,** 1070 (1960).
(7) Leussing, D. L., Newman, L., *J. Am. Chem. Soc.* **78,** 552 (1956).
(8) McCormick, B. J., Gorin, G., *Inorg. Chem.* **1,** 691 (1962).
(9) Michaelis, L., Schubert, M. P., *J. Am. Chem. Soc.* **52,** 4418 (1930).
(10) Saffir, P., Taube, H., *Ibid.,* **82,** 13 (1960).
(11) Schubert, M. P., *Ibid.,* **54,** 4077 (1932).
(12) Stern, K. G., Du Bois, D. J., *Biol. Chem.* **116,** 575 (1954).
(13) Tischer, T. N., Ph.D. thesis, Department of Chemistry, University of Wisconsin, 1961.

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Redox Reactions of Ligands

I. Oxidation of Oxalato Complexes of Chromium(III) by Cerium(IV) in Aqueous Sulfuric Acid

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The cerium(IV) oxidations of $Cr(C_2O_4)_3^{-3}$, cis-$Cr(OH_2)_2(C_2O_4)_2^-$, and $Cr(OH_2)_4C_2O_4^+$ have been investigated in aqueous acidic-sulfate media. The observations are consistent with the reactions proceeding, at least initially, according to the stoichiometries: $Cr(C_2O_4)_3^{-3} \xrightarrow{2Ce(IV)}$ *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ + $2CO_2$; *cis*-$Cr(OH_2)_2(C_2O_4)_2^- \xrightarrow{2Ce(IV)} Cr(OH_2)_4C_2O_4^+$ + $2CO_2$; and $Cr(OH_2)_4C_2O_4^+ \xrightarrow{2Ce(IV)} Cr(OH_2)_6^{+3} + 2CO_2$. In moderately strong sulfuric acid each redox reaction appears to follow the simple rate law $-d[Ce(IV)]/dt = k[Cr(III)complex]\,[Ce(IV)]$. The values of k in 1.83M sulfuric acid at 25° for $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(S_2O_4)_2^-$, and $Cr(OH_2)_4C_2O_4^+$ are, respectively, $1.27(\pm 0.14) \times 10^{-1}$, $1.06 (\pm 0.10) \times 10^{-1}$, and $7.5(\pm 0.9) \times 10^{-3}$ liter mole^{-1} sec^{-1}. The cerium(IV) oxidation of *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ has been examined in further detail. As the acidity is diminished at constant sulfate ion concentration, deviations from simple second-order behavior develop, primarily because of an increasing inhibition of the reaction by cerium(III). For each of several acidic-sulfate media studied, the results for a range of conditions may be summarized by the more general rate law $-d[Ce(IV)]/dt = k'[cis^-]\,[Ce(IV)]^2/k''[Ce(III)] + k'''[Ce(IV)]$, where values of the constants are characteristic for the particular medium. This result is interpreted on the basis of the simple mechanism: $cis^- + Ce(IV) \underset{fast}{\overset{slow}{\rightleftharpoons}} cis^\circ + Ce(III)$; $cis^\circ + Ce(IV) \xrightarrow{fast}$ products where cis° is an intermediate formed by the one-equivalent oxidation of *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$. Detailed interpretations are discussed with reference to the rates and mechanisms of related reactions.

In redox reactions between labile metal ions (hydrated or otherwise complexed) and anionic or neutral reagents, the formation of intermediate metal-ligand complexes has been demonstrated or proposed in a number of cases (*4*, *13*, *24*, *46*), yet much remains to be learned about the importance, properties, reactivities, and primary decomposition products of such intermediates. Considerably less attention has been devoted to reactions of nonlabile metal-ligand complexes in which ligands are oxidized or reduced by external reagents, by other parts of the complex, or by both. Some classic examples of these reactions are recorded by Werner (*45*); more recent investigations of such reactions have been reported (*10*, *26*, *28*, *31*, *37*, *38*, *48*).

For reactions of these types, the identity of the ligand, its environment within the complex—e.g., the nature of the central metal and the properties and positions of the other ligands—and the character of any external redox reagent are important variables which will influence the thermodynamic feasibility of processes, the products formed under given experimental conditions, and the rates and mechanisms of redox processes. Within this framework some significant problems await solution.

In the present investigation, which represents the first of a series of studies being undertaken in this laboratory on redox reactions of ligands, we have examined the reactions of $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, and $Cr(OH_2)_4C_2O_4^+$ with cerium(IV) in aqueous acidic media. Each reactant system involves a nonlabile complex ion containing an oxidizable ligand, and an oxidant known to be capable of attacking both the isolated ligand (*3*, *8*, *14*, *36*, *46*) and the parent aquo cation (*43*, *47*). All experiments were performed in the presence of an excess of sulfuric acid, in which medium the cerium(IV) exists very predominantly as mononuclear sulfato (or bisulfato) complexes (*19*, *43*).

Under the chosen experimental conditions the reaction between $Cr(OH_2)_4C_2O_4^+$ and cerium(IV) is sufficiently slow to be neglected in kinetic studies of the early stages of the reaction between *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ and cerium(IV). On the other hand, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ and $Cr(C_2O_4)_3^{-3}$ react with cerium(IV) at comparable rates, and the reaction of *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ must be taken into consideration in establishing the rate at which $Cr(C_2O_4)_3^{-3}$ reacts. It has thus been appropriate to devote major attention at this time to the cerium(IV) oxidation of *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$.

Experimental

Materials. Unless otherwise specified, chemicals were of reagent grade. For the majority of experiments doubly distilled water was used, the second distillation being made in a borosilicate glass apparatus after the water had been refluxed with potassium dichromate and sulfuric acid for several hours. The kinetic data for the singly and doubly distilled water were identical within the usual limits of error. Most stock cerium(IV) sulfate solutions were prepared from G. F. Smith Chemical Co. standard ceric sulfate solution [approximately $0.1N$ cerium(IV) in $1N$ sulfuric acid]. Identical kinetic results were obtained in experiments where cerium(IV) sulfate solutions were prepared by converting Anachemia Chemicals Ltd. ammonium hexanitratocerate(IV) to cerium(IV) hydroxide with aqueous ammonia solution and dissolving the well washed precipitate in sulfuric acid. All cerium(IV) stock solutions were standardized by titration against arsenious oxide using established procedures (*44*). Concentrations of cerium(III) in the standard cerium(IV) solutions, which amounted to ~4% of the total cerium, were determined from the total absorbance at 320 mμ after oxidation of the cerium(III) with potassium persulfate (*11*, *30*). Stoichiometric concentrations of acid in the standard cerium(IV) solutions were measured by direct alkaline titration, taking into account the hydroxide consumed by precipitation of the cerium. Standard cerium(III) sulfate solutions were prepared by the reaction of equivalent amounts of standard cerium(IV) sulfate and standard oxalic acid.

Standard solutions of sulfuric acid and sodium bisulfate were used to adjust the concentrations of hydrogen ion, bisulfate ion, and sulfate ion. [The concentrations of hydrogen ion, bisulfate ion, and sulfate ion were computed by using the calculations of Baes (*2*) on the bisulfate ion dissociation in sulfuric acid–sodium sulfate solutions.] The concentrations of sodium ion and available hydrogen ion in the standard sodium bisulfate solution were found to be equivalent. The sodium ion content was determined by titration of the acidity after washing samples of solutions through carefully prewashed cation exchange resin in the hydrogen form. The cation exchange resin used for these and other purposes was Dowex 50-X8; the anion exchange resin used throughout the study was Dowex 1-X8.

Solutions containing the *cis*-bisoxalatodiaquochromate(III) ion were made by first preparing the readily crystallizable potassium *trans*-bisoxalatodiaquochromate(III) from oxalic acid and potassium dichromate by the method of Werner (*39*). Portions of the recrystallized trans salt were dissolved in water, and resulting solutions were passed through cation exchange resin in the sodium form, to replace the potassium ion by sodium ion and to remove any cationic chromium(III) species, and through anion exchange resin in the perchlorate form to remove any highly charged anionic chromium(III) species. The analysis of effluent solutions for chromium by the method of Haupt (*20*) as described by Altman and King (*1*), and for oxalate by a method similar to that described by Hamm (*17*), gave chromium-oxalate ratios of the order of 1.00 to 2.02. To ensure essentially complete isomerization of the trans to the cis isomer, the solutions were allowed to stand overnight before being used in kinetic experiments (*7*, *17*).

Solutions containing the mono-oxalatotetraaquochromium(III) ion were prepared by reaction of the hexaaquochromium(III) ion with oxalic acid. A solution which was 0.1000*M* in hexaaquochromium(III) perchlorate and 0.100*M* in perchloric acid was first prepared by the reaction of hydrogen peroxide with a solution containing calculated amounts of potassium dichromate and perchloric acid. After the excess peroxide had been destroyed by prolonged boiling, the solution was stored overnight at 0°, the potassium perchlorate which crystallized was filtered off and washed with ice-cold water, and the filtrate with washings was diluted to the required volume. Solutions which contained equimolar amounts of the hexaaquochromium(III) perchlorate and oxalic acid were heated to incipient boiling for about an hour. The cooled solutions were passed through anion exchange resin in the perchlorate form to remove anionic impurities, and through cation exchange resin in the hydrogen form to remove unreacted hexaaquochromium(III) ion. Effluent solutions were placed on another column containing cation exchange resin in the hydrogen form, and the column was eluted with 0.3*M* perchloric acid. Middle fractions of the chromium(III)-containing effluent solutions were retained and portions were analyzed for chromium and oxalate as before (*1*, *17*, *20*) and for hydrogen ion by measuring the total acidity of an aliquot after it was passed through a column containing cation exchange resin in the hydrogen form. The hydrogen ion generated by the mono-oxalatotetraaquochromium(III) ion was taken into consideration. Within $\sim 2\%$, chromium-oxalate ratios of 1 to 1 were obtained. Perchlorate was removed from the mono-oxalatotetraaquochromium(III) solution by adding an equivalent quantity of potassium sulfate, storing the solution overnight at 0°, and quantitatively filtering off the potassium perchlorate. Further analysis for chromium, oxalate, and hydrogen ion confirmed a chromium-oxalate ratio of very close to 1 to 1, established the hydrogen ion concentration, and demonstrated that negligible quantities of potassium perchlorate remained in solution.

A portion of the solution was subjected to a qualitative electrical migration experiment using a three-component cell similar to that described by Hardwick and Robertson (*19*). The solution under investigation was placed in the center compartment, and in the outer compartments were placed sulfuric acid solutions of concentrations similar to that of the test solution. No diffusion occurred over a period of 24 hours. Application of about 50 volts d.c. across the electrodes caused migration of violet color to the cathode and no violet color to the anode. The results indicate a positively charged chromium species.

Potassium trisoxalatochromate(III) was prepared by Graham's method (*15*), as described by Palmer (*32*). Solutions of the recrystallized salt, used for studies on the trisoxalatochromate(III) ion, were standardized by analysis for chromium as before (*1*, *20*).

Stoichiometries. From preliminary observations on the reactions between cerium(IV) and each of $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, and $Cr(OH_2)_4C_2O_4^+$ it was evident that carbon dioxide is evolved, as identified by precipitation of barium carbonate from barium hydroxide solution. It was also evident that cerium(IV) is reduced to cerium(III), as demonstrated by disappearance of the characteristic cerium(IV) color and the ability of solutions to oxidize iodide ion. Spectral analyses and qualitative tests showed that no dichromate is formed until all the oxalate has been consumed.

The stoichiometry of the cerium(IV) reaction with *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ was investigated by quantitative and additional qualitative examination of the reaction products.

A stream of nitrogen, which had been freed from any traces of carbon dioxide by first passing through alkaline solution, was used to sweep the carbon dioxide from a reaction mixture (initially carbon dioxide–free) prepared from equivalent amounts of potassium *cis*-bisoxalatodiaquochromate(III) and cerium(IV) sulfate in 1.70*M* sulfuric acid. The issuing nitrogen stream was allowed to pass through a measured volume of standard barium hydroxide solution. After the reaction had proceeded essentially to completion, the barium hydroxide solution was filtered to remove barium carbonate and was then titrated with standard sulfuric acid, using methyl orange as indicator. (Five hours at 35° were allowed, this condition being estimated to be adequate from a consideration of relevant kinetic data.)

The amount of carbon dioxide evolved during the oxidation was calculated to be 96% of the theoretical amount which would correspond to the oxidation of one oxalate to carbon dioxide per chromium. The reaction vessel was observed to contain a violet solution, and white precipitate which had begun to appear only after the reaction had been proceeding for some time.

The solution and precipitate were separated by filtration. Qualitative analysis of the precipitate showed that it contained cerium(III) and sulfate ion. [No precipitate appeared when *cis*-bisoxalatodiaquochromate(III) ion and cerium(IV) were allowed to react at this acidity under conditions where the sulfate and/or cerium concentrations were somewhat lower.] The filtrate, including washings, was diluted to a measured volume, and two measured aliquots of this solution were withdrawn for study. The first aliquot was passed onto a cation exchange column in the hydrogen form. Elution with 1*M* sulfuric acid left a small dark violet band of hexaaquochromium(III) ion at the top of the column, while the rest of the chromium passed through the column. [In separate experiments it was confirmed that the $Cr(OH_2)_6^{+3}$ ion is retained as a dark violet band at the top of the resin when the resin is eluted with 1*M* sulfuric acid. This is in agreement with the observations of King and Dismukes (*23*).] Analysis of the effluent solution showed that 4 to 5% of the chromium had been retained by the column.

The second aliquot was passed onto another cation exchange resin and eluted as before, the effluent solution was passed onto a second cation exchange column, and the elution process was repeated. No dark band was left on the second column, and analysis of a portion of the new effluent solution showed that there had been no further loss of chromium on passage through the second column. Two additional portions of the last-mentioned solution were withdrawn for examination. The first portion was analyzed for oxalate, as before, and chromium-oxalate ratios of 1.00 to 1.02 were obtained. The spectrum of the second portion was measured through the visible range and found to agree well with the spectrum of the mono-oxalatotetraaquochromium (III) ion at the same chromium concentration.

Some critical experiments of the type described above were repeated, and similar results were obtained. The observations are consistent with the following stoichiometry for the initial reaction:

$$cis\text{-}Cr(OH_2)_2(C_2O_4)_2^- + 2Ce(IV) + 2H_2O \rightarrow Cr(OH_2)_4C_2O_4^+ + 2Ce(III) + 2CO_2 \quad (1)$$

The production of the small amounts of hexaaquochromium(III) ion described above suggests that the further Reaction 2 occurs

$$Cr(OH_2)_4C_2O_4^+ + 2Ce(IV) + 2H_2O \rightarrow Cr(OH_2)_6^{+3} + 2Ce(III) + 2CO_2 \quad (2)$$

but that the specific rate for this reaction is less than that for Reaction 1. This indication of the relative reactivities of $Cr(OH_2)_4C_2O_4^+$ and *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ toward cerium(IV) is confirmed by kinetic experiments described below. In addition, support for the stoichiometry specified by Reaction 2 is provided by agreement between the rates of cerium(IV) consumption by $Cr(OH_2)_4C_2O_4^+$ as measured directly by titrimetry and as measured by spectrophotometry on the basis that $Cr(OH_2)_6^{+3}$ is the only absorbing chromium product.

For the initial reaction between $Cr(C_2O_4)_3^{-3}$ and cerium(IV) the most obvious stoichiometry is:

$$Cr(C_2O_4)_3^{-3} + 2Ce(IV) + 2H_2O \rightarrow cis\text{-}Cr(OH_2)_2(C_2O_4)_2^- + 2Ce(III) + 2CO_2 \quad (3)$$

This view receives support, in a similar way, from the observations that the initial rates of cerium(IV) consumption by $Cr(C_2O_4)_3^{-3}$, as measured directly by titrimetry, agree well with those obtained by spectrophotometry on the assumption that *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ is the only absorbing chromium product. The composition of a reactant system initially containing $Cr(C_2O_4)_3^{-3}$ and cerium(IV) soon becomes complicated, however, since $Cr(C_2O_4)_3^{-3}$ and *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ react with cerium(IV) at comparable rates.

Measurement of Reaction Rates by Spectrophotometry. The rates of reaction were measured with a Beckman Model DU spectrophotometer. The observations were made at 480 mμ, at which wave length the molar absorptivity coefficients for the cerium(IV) in the chosen media are significantly greater than the coefficients for the oxalatochromium(III) complexes or for the $Cr(OH_2)_6^{+3}$ ion. During the course of reaction solutions were kept in 1-cm. quartz cells which were held at the required temperature to within ±0.1°. For a given rate determination two solutions were prepared, one containing the chromium salt and the other containing the cerium(IV) sulfate, sulfuric acid, and any required sodium bisulfate. The two constituent solutions were brought to the required temperature in a thermostat, rapidly mixed, and quickly introduced into a clean, dry thermostated cell in the spectrophotometer. (For the experiments in 1.83*M* sulfuric acid, part of the acid was added to the solution of the chromium salt, shortly before final thermostating, in order to avoid excessive heating on mixing the reactant solutions. For the other acidities studied this precaution was not necessary. On mixing equal volumes of 1*M* sulfuric acid and water at 25° the temperature increased by only 0.12 ±0.02°.)

The absorbance at 480 mμ was measured 1 minute after mixing the solutions, and thereafter at appropriate intervals.

Interest was generally centered on the first stages of reaction. In the times involved no turbidity appeared in reactant solutions, even for the highest sulfate ion and cerium concentrations and for the lowest hydrogen ion concentrations. For each kinetic run the sulfate ion concentration was buffered by large and thus essentially constant concentrations of hydrogen ion and bisulfate ion; therefore the distribution of cerium(IV) among various sulfato (or bisulfato) complexes remained essentially constant throughout each run (*19*, *43*). Under this condition of a constant medium each species absorbing at 480 mμ—cerium(IV), $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, $Cr(OH_2)_4C_2O_4^+$, and $Cr(OH_2)_6^{+3}$—was shown to obey Beer's law throughout the relevant concentration range of about 2×10^{-2} to $1 \times 10^{-3}M$. In 1.83*M* sulfuric acid the molar absorptivity coefficients of $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, $Cr(OH_2)_4C_2O_4^+$, and $Cr(OH_2)_6^{+3}$ at 480 mμ and a slit width of 0.015 mm. were measured and found to be 16.1, 15.2, 11.0, and 3.1. While the absorptivity coefficients for these chromium ions changed only very slightly with changes in the medium, the coefficient for the cerium(IV) was noticeably dependent on the medium and values were determined for each set of conditions used. In 1.83*M* sulfuric acid the absorptivity coefficient of the cerium(IV) at 480 mμ and a slit width of 0.015 mm. was found to be 24.0. Since the absorbances of the cerium(IV) solution are significantly altered by small changes in wave length in the region of 480 mμ, it was convenient to adjust the wave length setting before any series of measurements, so that a stock solution which was 0.0100*M* in cerium(IV) and 1.83 *M* in sulfuric acid gave an absorbance of 0.240 at a slit width of 0.015 mm. The same slit width was maintained throughout the series of measurements.

The method of establishing the concentrations of reactant species from the measured absorbances at various times during the early stages of reaction will be illustrated for the cerium(IV) reaction with *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$.

At zero time, the absorbance at 480 mμ could be attributed to the cerium(IV) and the *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ ion alone. Thus

$$A_0 = e_{Ce}[Ce(IV)] + e_{cis}[cis^-] \quad (4)$$

where A is the absorbance, square brackets indicate concentrations in moles per liter, zero subscripts indicate zero time, and e_{Ce} and e_{cis} are absorptivity coefficients, e_{Ce} being an average for the various cerium(IV) species in solution. Values of A_0, calculated from the absorbances of the components using Beer's law, agreed with the values obtained by extrapolating the measured absorbances back to zero time, a result which indicates that any intermediate complexes which may be formed between cerium(IV) and *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ are not spectrally detectable at 480 mμ.

At any time, t, it was assumed that

$$A_t = e_{Ce}[Ce(IV)]_t + e_{cis}[cis^-]_t + e_{mono}[mono]_t \quad (5)$$

Also, from the stoichiometry of Reaction 1 it is true that, at time t,

$$[Ce(IV)]_0 - [Ce(IV)]_t = 2([cis^-]_0 - [cis^-]_t) = 2[mono]_t \quad (6)$$

Then, under conditions where $2[cis^-]_0 \geqslant [Ce(IV)]_0$, it is readily shown from Equations 4, 5, and 6 that

$$[Ce(IV)]_t = [Ce(IV)]_0(A_t - A_\infty)/(A_0 - A_\infty) \quad (7)$$

where A_∞ is the value the absorbance would have if Reaction 1 were to proceed to completion. Under conditions where $2[cis^-]_0 \leqslant [Ce(IV)]_0$, it is likewise readily shown that

$$[cis^-]_t = [cis^-]_0(A_t - A_\infty)/(A_0 - A_\infty) \quad (8)$$

The appropriate Equations 7 or 8 and Equation 6 were used to calculate values of $[Ce(IV)]_t$ and $[cis^-]_t$ from the measured values of A_t. The values of A_0 used were those obtained by extrapolation to $t = 0$, and the values of A_∞ were those calculated for $t = \infty$. The calculated values of A_∞ agreed within a few per cent with values measured after reactions had been allowed to go to completion. The observations are consistent with the data presented above on the amount of $Cr(OH_2)_6^{+3}$ produced and on the absorptivity coefficients of the cerium(IV) and of *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, $Cr(OH_2)_4C_2O_4^+$, and $Cr(OH_2)_6^{+3}$.

The same principles were used to observe by spectrophotometry the initial stages of the reactions of $Cr(C_2O_4)_3^{-3}$ and $Cr(OH_2)_4C_2O_4^+$ with cerium(IV). For these purposes the respective stoichiometries defined by Reactions 3 and 2 were assumed.

Measurement of Reaction Rates by Titrimetry. The rates of cerium(IV) consumption by each of $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, and $Cr(OH_2)_4C_2O_4^+$ were also measured by a direct titrimetric method. Solutions were prepared and mixed as for the spectrophotometric procedure. At appropriate times aliquots of the reactant solutions were quenched with known volumes of standard ferrous sulfate, and the excess ferrous ion was titrated potentiometrically with standard potassium dichromate.

It was established that unreacted oxalato complex, $Cr(OH_2)_6^{+3}$, and free oxalate do not interfere in the titration. Thus the concentrations of cerium(IV) could be readily measured as a function of time.

The rates of cerium(IV) consumption by $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, and $Cr(OH_2)_4C_2O_4^+$ in 1.83*M* sulfuric acid, as measured by the spectrophotometric and titrimetric procedures, are compared in Figure 1. For *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ the agreement between the two experimental procedures is excellent throughout the reaction period studied, while for $Cr(OH_2)_4C_2O_4^+$ and $Cr(C_2O_4)_3^{-3}$ the agreement is probably as good as can be expected. For $Cr(C_2O_4)_3^{-3}$ the cerium(IV) concentrations have been calculated in this case without taking into account the reaction of the *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, the first reaction product, with cerium(IV). For establishing the rate constant for the $Cr(C_2O_4)_3^{-3}$ reaction the titrimetric method was used, and appropriate consideration was given to this further reaction (see below). The rate constant for the $Cr(OH_2)_4C_2O_4^+$ reaction was likewise established with the use of the titrimetric procedure.

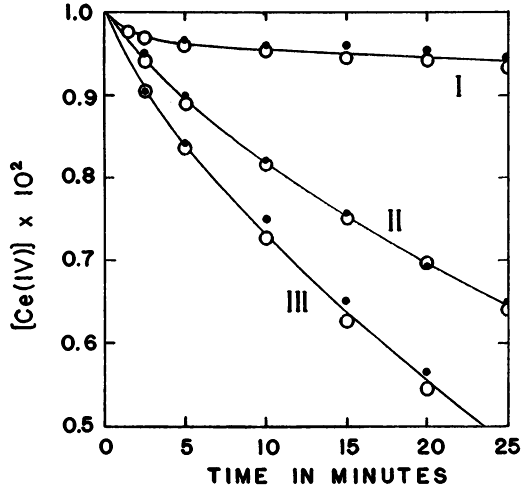

Figure 1. Cerium(IV) consumption in 1.83M sulfuric acid

○ *Spectrophotometry*
● *Titrimetry*

I. $Cr(OH_2)_4C_2O_4^+$
II. *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$
III. $Cr(C_2O_4)_3^{-3}$
$[Ce(IV)]_0 = 1.00 \times 10^{-2}M$
$[Cr(III)complex]_0 = 5.00 \times 10^{-3}M$
$T = 25°$

The possible influence of oxygen was checked by using the titrimetric method to study the consumption of cerium(IV) by *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ in the absence of oxygen. Component solutions were introduced into a closed container, flushed with nitrogen, and without exposure to the atmosphere, mixed, and allowed to react. The usual method for quenching was used. Comparison of the results for a series of solutions studied in this way with the results for similar solutions studied by the ordinary procedure indicated that the exclusion of oxygen has no measurable effect on the rate of the reaction.

Kinetic Results

Reactions in 1.83*M* Sulfuric Acid. In a medium of 1.83*M* sulfuric acid the reaction of *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ with cerium(IV) was found to be of apparent second order, being first order in each reactant. Second-order rate plots based on spectrophotometric measurements at 25° are shown in Figure 2. The average of 11 kinetic runs which covered the reactant concentration ranges $[Ce(IV)]_0 = 2.00 \times 10^{-2}$ to $2.50 \times 10^{-3}M$ and $[cis^-]_0 = 1.00 \times 10^{-2}$ to $2.50 \times 10^{-3}M$ gave a mean value for the apparent second-order rate constant, k $(= -\{d[Ce(IV)]/dt\}/[Ce(IV)][cis^-])$ of 1.06 $(\pm 0.10) \times 10^{-1}$ liter mole^{-1} sec.$^{-1}$ The value in parenthesis refers to the standard deviation from the mean.

In the same medium the reactions of both $Cr(C_2O_4)_3^{-3}$ and $Cr(OH_2)_4C_2O_4^+$ with cerium(IV) were found by both spectrophotometry and titrimetry to be also of apparent

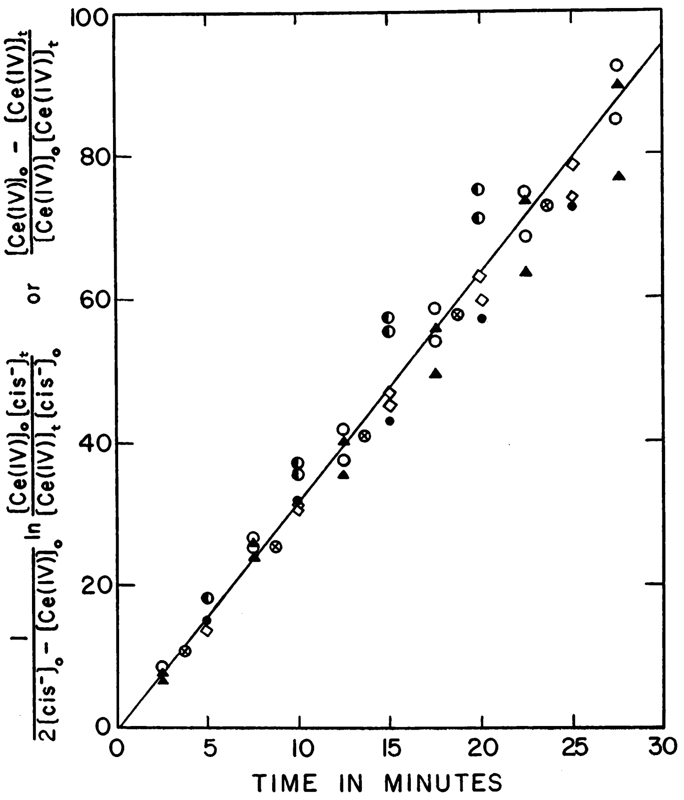

Figure 2. Second-order rate plot for reaction of cis-$Cr(OH_2)_2$-$(C_2O_4)_2^-$ with cerium(IV) in 1.83M sulfuric acid at 25°

Where $[Ce(IV)]_0 \neq 2[cis^-]_0$, ordinate = $\{1/2[cis^-]_0 - [Ce(IV)]_0\}$ $ln\{[Ce(IV)]_0[cis^-]_t/[Ce((IV)]_t[cis^-]_0\}$
Where $[Ce(IV)]_0 = 2[cis^-]_0$, ordinate = $\{[Ce(IV)]_0 - [Ce(IV)]_t\}/[Ce(IV)]_0[Ce(IV)]_t$

◇ $[Ce(IV)]_0 = 1.00 \times 10^{-2}M$, $[cis^-]_0 = 1.00 \times 10^{-2}M$
◐ $[Ce(IV)]_0 = 1.00 \times 10^{-2}M$, $[cis^-]_0 = 5.00 \times 10^{-3}M$
● $[Ce(IV)]_0 = 1.00 \times 10^{-2}M$, $[cis^-]_0 = 2.50 \times 10^{-3}M$
○ $[Ce(IV)]_0 = 2.50 \times 10^{-3}M$, $[cis^-]_0 = 5.00 \times 10^{-3}M$
▲ $[Ce(IV)]_0 = 5.00 \times 10^{-3}M$, $[cis^-]_0 = 5.00 \times 10^{-3}M$
⊗ $[Ce(IV)]_0 = 2.00 \times 10^{-2}M$, $[cis^-]_0 = 5.00 \times 10^{-3}M$

second order, again showing first-order dependence on each reactant. The apparent second-order rate constant for $Cr(C_2O_4)_3^{-3}$ was obtained from titrimetric measurements by the method of French (*12*), assuming the *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ produced undergoes a competitive second-order reaction with the $Cr(C_2O_4)_3^{-3}$. The value of the constant at 25° was found to be $1.27(\pm 0.14) \times 10^{-1}$ liter mole^{-1} sec.$^{-1}$ The apparent second-order rate constant for the $Cr(OH_2)_4C_2O_4^+$ reaction with cerium(IV) at 25° was found from the titrimetric measurements to be $7.5(\pm 0.9) \times 10^{-3}$ liter mole^{-1} sec.$^{-1}$

Additional Studies on *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ Reaction. The kinetics of the *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ reaction with cerium(IV) have been investigated in further detail.

While the reaction exhibits good second-order behavior in 1.83*M* sulfuric acid, the theoretically linear second-order rate plots develop marked curvature at lower acidities. This observation is illustrated by Figure 3, where the second-order plots are shown for the reaction in 0.950*M* sulfuric acid, and for two media of lower acidity but with the same calculated sulfate ion concentration. The detailed compositions of the solutions are indicated by the legend to Figure 3 and by Table I. The curvature arises, principally, from an inhibition of the reaction by cerium(III). This inhibition is demonstrated in Figure 4, which shows the cerium(IV) consumption in 0.950*M* sulfuric acid containing various amounts of cerium(III) in the initial reaction mixture.

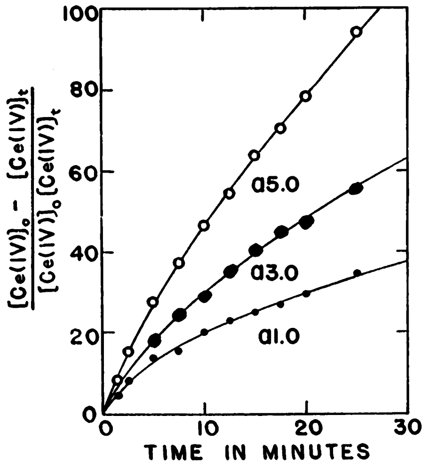

Figure 3. Second-order rate plots for reaction of cis-$Cr(OH_2)_2(C_2O_4)_2^-$ with cerium(IV)

For each solution $[cis^-]_0 = 5.00 \times 10^{-3}M$, $[Ce(IV)]_0 = 1.00 \times 10^{-2}M$, $[Ce(III)]_0 = 0.04 \times 10^{-2}M$, and $T = 25°$. Compositions of three media indicated in Table I

Table I. Composition of Three Sulfuric Acid–Sodium Sulfate Media

Solution Series	*Stoichiometric Concentrations*		*Equilibrium Concentrations (2)*			*Ionic Strength*
	$[H_2SO_4]$	*$[Na_2SO_4]$*	*$[HSO_4^-]$*	*$[H^+]$*	*$[SO_4^{-2}]$*	
a5	0.950	—	0.675	1.225	0.276	1.50
a3	0.683	0.170	0.578	0.788	0.276	1.40
a1	0.429	0.286	0.439	0.419	0.276	1.27

In separate experiments it was observed that the addition of lanthanum(III) or aluminum(III) at similar and somewhat higher concentration levels to the cerium(III) had no detectable effect on the reaction rate.

The above observations clearly indicate the inadequacy of the simple second-order law for describing the reaction rate outside the conditions of strongly acidic solutions and low initial cerium(III) concentrations. A more general rate law, suggested by considerations of the reaction mechanism (see Discussion), which takes into account the inhibiting effect of cerium(III), is of the form

$$\frac{-d[\mathrm{Ce(IV)}]}{dt} = \frac{k'[\mathrm{cis}^-][\mathrm{Ce(IV)}]^2}{k''[\mathrm{Ce(III)}] + k'''[\mathrm{Ce(IV)}]} \tag{9}$$

For appropriate relative values of the two denominator terms, this expression will reduce to the simple second-order rate law. Equation 9 may be rewritten in the form

$$\frac{-[\mathrm{Ce(IV)}][\mathrm{cis}^-]}{d[\mathrm{Ce(IV)}]/dt} = \frac{k''[\mathrm{Ce(III)}]}{k'[\mathrm{Ce(IV)}]} + \frac{k'''}{k'} \tag{10}$$

In Figure 5 the left side of Equation 10 has been plotted against values of [Ce(III)]/[Ce(IV)] for three series of solutions, each series corresponding to one of the sulfuric acid–sodium sulfate media given in Table I. Series a5 refers to the same solutions used for the construction of Figure 4, while series a3 and a1 refer to similar sets of solutions [also containing different initial cerium(III) concentrations] in the other two media. For each solution values of d[Ce(IV)]/dt were determined for several reaction times from the curve of [Ce(IV)] *vs.* time. Points of the same type in Figure 5 refer to a single solution. For series a5 points for each solution correspond to up to 30% reaction. A satisfactory linear relation is found in agreement with the proposed rate law.

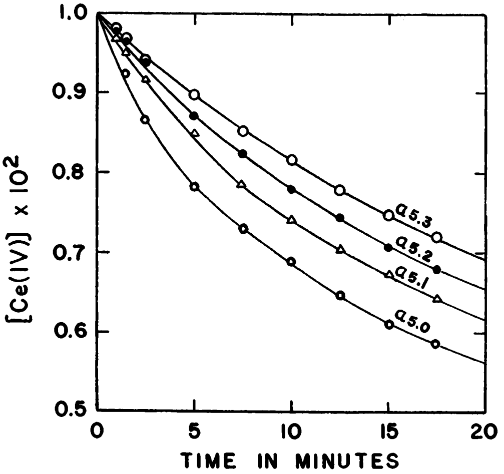

Figure 4. Effect of cerium(III) on cerium(IV) -cis-$Cr(OH_2)_2(C_2O_4)_2^-$ reaction in 0.950M sulfuric acid

$[Ce(IV)]_0 = 1.00 \times 10^{-2}M$, $[cis^-]_0 = 5.00 \times 10^{-3}M$, $T = 25°$

Solution a5.0. $[Ce(III)]_0 = 0.04 \times 10^{-2}M$
Solution a5.1. $[Ce(III)]_0 = 0.29 \times 10^{-2}M$
Solution a5.2. $[Ce(III)]_0 = 0.54 \times 10^{-2}M$
Solution a5.3. $[Ce(III)]_0 = 0.79 \times 10^{-2}M$

For series a3 points have been limited to 20% reaction for any one solution; for series a1 points have been limited to 10% reaction. Within these limits satisfactory linear relations are also obtained for these two series. Outside the specified limits for series a3 and a1 there was a tendency for points to lie above the lines represented. However, for some solutions of series a3 and for most solutions of series a1, some turbidity developed after the reaction had progressed for some time. In summary, for solutions of series a5 the suggested rate law appears to hold through to the middle stages of reaction, while for solutions of series a3 and a1 it holds for the early stages of reaction. From Figure 5 it is fairly clear that the values of k'''/k' and k''/k' are a function of the reaction medium.

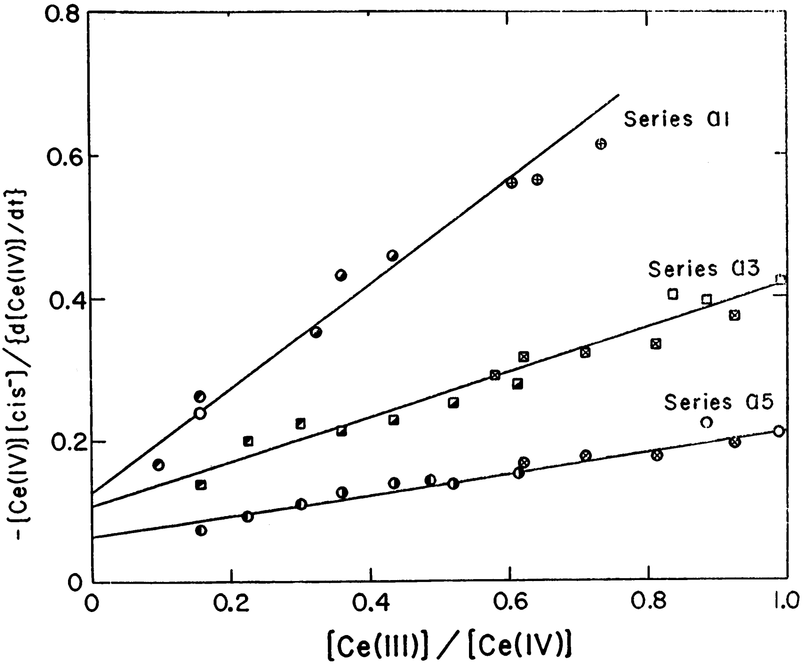

Figure 5. Test of rate law for cerium(IV)-cis-$Cr(OH_2)_2(C_2O_4)_2^-$ reaction

Discussion

It is apparent that $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, and $Cr(OH_2)_4C_2O_4^+$ react smoothly with cerium(IV) in acidic-sulfate media, 1 mole of oxalate being oxidized for each 2 moles of cerium(IV) consumed. The observations made are consistent with the view that the three reactions proceed, at least initially, according to the stoichiometries represented by the respective Reactions 3, 1, and 2. The initial absorbances of reactant solutions (values obtained by extrapolation of measured absorbances to zero time) agree well with the values calculated, on the basis of Beer's law, from the absorptivity coefficients of the components. Further, as the reactions in 1.83*M* sulfuric acid proceed, the absorbances of the solutions move toward the values expected for the assumed products at rates which demonstrate the reactions are first order in cerium(IV) and complex—see, for example, Figure 2. We thus find no indication that reaction intermediates contribute measurably to the absorbances of reactant solutions, or that reaction conditions cause the rapid equilibration of any of the oxalato complexes with other species of chromium(III) and oxalate. There remains a possibility that some sulfate may enter the coordination sphere of the chromium in place of water, especially in the case of the slower cerium(IV)-$Cr(OH_2)_4C_2O_4^+$ reaction. [Fogel, Tai, and Yarborough (*9*) have reported recent work on chromium(III)-sulfato complexes.] This matter is still being studied. That this possibility can have no significant effect on the spectrophotometric kinetic studies is demonstrated by the agreement between the results obtained by use of this method and those obtained by the titrimetric procedure.

For each of the three redox reactions, the apparent second-order behavior in 1.83*M* sulfuric acid implies the activated complex for the rate-determining step will have a composition $(Cr)(C_2O_4)_n(Ce)^{7-2n}$ together with unspecified numbers of H_2O, H^+, and SO_4^{-2}, where *n* is the value appropriate to the original oxalato complex. The possibility that the rate-determining step involves reaction of cerium(IV) with free oxalate is clearly excluded by the form of the rate law and by the slow rates at which chromium(III)-oxalato complexes aquate (*25*) and exchange bound with free oxalate (*16*, *25*, *27*, *29*). Thus Krishnamurty and Harris (*25*) have shown that $Cr(OH_2)_2(C_2O_4)_2^-$ does not aquate at a measurable rate under moderate conditions, and that the exchange of labeled carbon between $Cr(OH_2)_2(C_2O_4)_2^-$ and $C_2O_4^{-2}$ at 50° and pH 1 is less than 5% in 6 hours. These findings are consistent with the observation that the spectrum of *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ in aqueous solution remains constant for long periods of time (*7*, *17*), a result which we have confirmed for the acidic conditions under which our studies were made. In the case of $Cr(C_2O_4)_3^{-3}$ the aquation rate is measurable and increases with increased acidity (*25*); nevertheless the process remains too slow to be of importance in the $Cr(C_2O_4)_3^{-3}$–cerium(IV) reaction.

Thus, for the conditions where second-order behavior is observed, the chemical circumstances indicate the cerium(IV) oxidation of each chromium complex will involve a rate-determining one-equivalent oxidation of the complex ion (or a species in rapid equilibrium with the complex ion) to an intermediate, followed by the rapid one-equivalent oxidation of the intermediate. Without reference to the role of water coordinated to the chromium, the most obvious mechanism in accord with these specifications is:

$$Cr(C_2O_4)_n^{3-2n} + Ce(IV) \xrightarrow{\text{slow}} Cr(C_2O_4)_n^{4-2n} + Ce(III) \tag{11}$$

$$Cr(C_2O_4)_n^{4-2n} + Ce(IV) \xrightarrow{\text{rapid}} Cr(C_2O_4)_{n-1}^{5-2n} + Ce(III) + 2CO_2 \tag{12}$$

[An alternative possibility would involve the initial production of $Cr(C_2O_4)_{n-1}$-$(CO_2)^{4-2n}$, CO_2, and Ce(III).]

An intermediate of type $Cr(C_2O_4)_n^{4-2n}$, which can be considered formally to involve either chromium(III) bound to $C_2O_4^-$ and to $n-1$ oxalates, or chromium(IV) bound to *n* oxalates, would be expected to react rapidly with cerium(IV). Considered as a complex of chromium(III), such an intermediate would be expected to aquate or undergo other substitution reactions slowly compared to direct reaction with cerium(IV). Considered as a complex of chromium(IV), such an intermediate would be expected to aquate and undergo other substitution reactions rapidly, but direct reaction with cerium(IV) should also be a rapid process. [The chromium(IV) and cerium(IV) could together perform the two-equivalent oxidation of an oxalate. Compare with the $Co(NH_3)_5C_2O_4^+$—Ce(IV) reaction (*37*).] The catalyzed release of significant amounts of bound oxalate would seem unlikely, however, in view of the quantitative observations made on the reaction products.

The more detailed studies on the cerium(IV)-*cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ reaction, which demonstrate deviations from simple second-order behavior and inhibition by cerium(III) at lower acidities, clearly show the need for some modification of the simple mechanism indicated by Reaction steps 11 and 12. The most obvious possibility, suggested by the retarding effect of cerium(III), is that Reaction 11 is reversible. The modified suggested mechanism for *cis*-$\mathrm{Cr(OH_2)_2(C_2O_4)_2^-}$ may then be represented as:

$$\mathrm{Cr(C_2O_4)_2^- + Ce(IV) \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Cr(C_2O_4)_2^{\circ} + Ce(III)} \tag{13}$$

$$\mathrm{Cr(C_2O_4)_2^{\circ} + Ce(IV) \xrightarrow{k_3} CrC_2O_4^+ + 2CO_2 + Ce(III)} \tag{14}$$

On the assumption that the concentration of $\mathrm{Cr(C_2O_4)_2^{\circ}}$ will remain very small, the steady-state approximation can be used, from which we obtain the rate expression

$$\frac{-d[\mathrm{Ce(IV)}]}{dt} = \frac{2k_1k_3[\mathrm{cis}^-][\mathrm{Ce(IV)}]^2}{k_2[\mathrm{Ce(III)}] + k_3[\mathrm{Ce(IV)}]} \tag{15}$$

Equation 15 has the same form as Equation 9, and the two equations may be identified if k''', k'', and k' are equated with k_3, k_2, and $2k_1k_3$, respectively. The plots in Figure 5 constitute a simple test of this modified rate law. The values of k_1 and of k_2/k_3 are apparently a function of the medium. Under conditions where $k_3[\mathrm{Ce(IV)}] \gg k_2[\mathrm{Ce(III)}]$ Equation 15 reduces to the simple second-order expression. This circumstance appears to be closely approached by the conditions which exist during the early stages of the reaction in 1.83*M* sulfuric acid if the initial cerium(III) concentration is low.

With reference again to Figure 5, one is tempted to ascribe the considerably different behaviors for the three series [especially the decrease in the inhibiting effect of the cerium(III) from series a1 to a5] to a specific function of hydrogen ion in the reaction. However, this matter requires very careful consideration. For example, the ionic strengths for the three series are not identical, and any attempt to adjust the ionic strengths to a single value, while maintaining constant sulfate ion concentration but different hydrogen ion concentrations, necessitates the inclusion of another electrolyte—e.g., $\mathrm{NaClO_4}$—which will doubtless influence the equilibrium quotients for the bisulfate dissociation. A detailed report on the role of hydrogen ion and sulfate ion in the cerium(IV)-*cis*-$\mathrm{Cr(OH_2)_2(C_2O_4)_2^-}$ reaction will be given in a separate communication (*42*) but a preliminary description of some of the results may be of interest.

To examine the possibility that the different kinetic behaviors for series a1, a3, and a5 may be due to differences in ionic strength, the solutions of series a1 and a3 were replaced by solutions of slightly different compositions in which small amounts of sodium perchlorate were included. Extreme assumptions about the way that the sodium perchlorate would affect the equilibrium quotients for the bisulfate dissociation were used to calculate the detailed compositions of the new solutions in order to maintain constant ionic strength at 1.50, constant sulfate ion concentration at 0.276*M*, and hydrogen ion concentrations close to those of solutions a1 and a3. No matter which of the assumptions was made in computing the compositions, the kinetic behaviors observed for the new solution series were very similar to those reported herein for series a1 and a3.

It becomes very reasonable, therefore, to attribute the different kinetic behaviors for series a1, a3, and a5, or for the new sets of series, to a specific role of hydrogen ion in the reaction. A more detailed form of the experimental rate law (Equation 9), which predicts quite well the relative values of the slopes and intercepts in the $-[\mathrm{Ce(IV)}]$-

[cis⁻]/{*d*[Ce(IV)]/*dt*} *vs.* [Ce(III)]/[Ce(IV)] curves for the solutions of different acidities, is of the form:

$$-\frac{d[\mathrm{Ce(IV)}]}{dt} = \frac{\bar{k}'[\mathrm{H}^+]^2[\mathrm{cis}^-][\mathrm{Ce(IV)}]^2}{k''[\mathrm{Ce(III)}] + \bar{k}'''[\mathrm{H}^+][\mathrm{Ce(IV)}]} \tag{16}$$

Such a rate law may be derived if one assumes that the activated complex for Reaction 13 incorporates a proton in addition to any held by the major species of *cis*-$\mathrm{Cr(OH_2)_2(C_2O_4)_2^-}$ and cerium(IV) in solution, and the activated complex for Reaction 14 incorporates two protons in addition to any held by the major species of *cis*-$\mathrm{Cr(OH_2)_2(C_2O_4)_2^-}$ and cerium(IV) in solution. Several plausible mechanisms are consistent with these requirements (*42*).

It is of interest to compare the influence of cerium(III) on the cerium(IV)–*cis*-$\mathrm{Cr(OH_2)_2(C_2O_4)_2^-}$ reaction with the similar retarding action by cerium(III) which Tong and King (*43*) found in their careful kinetic investigation of the cerium(IV) oxidation of $\mathrm{Cr(OH_2)_6^{+3}}$ in acidic-sulfate media. The observed rate law for the latter reaction may be written in the form

$$-\frac{d[\mathrm{Ce(IV)}]}{dt} = \frac{\bar{k}[\mathrm{Cr(III)}][\mathrm{Ce(IV)}]^2}{[\mathrm{Ce(III)}]}$$

There was, however, a faint indication that the denominator in the rate expression might be $\{[\mathrm{Ce(III)}] + \bar{k}''[\mathrm{Ce(IV)}]\}$. The relation between these observations and ours is striking. For the mechanism of the cerium(IV)–$\mathrm{Cr(OH_2)_6^{+3}}$ reaction Tong and King suggest a sequence of three one-equivalent reactions, with the second, the cerium(IV) oxidation of chromium(IV) to chromium(V), being rate-determining. The unimportance of the $\bar{k}''$ term in the denominator of their rate expression indicates that chromium(IV) is reduced to chromium(III) by cerium(III) more readily than it is oxidized to chromium(V) by cerium(IV). Tong and King suggest that a change of coordination number may be involved in the chromium(IV)–chromium(V) transformation as a possible reason for the bottleneck. For the cerium(IV)–*cis*-$\mathrm{Cr(OH_2)_2(C_2O_4)_2^-}$ reaction the term in cerium(IV) in the denominator of the rate law expression (Equation 9 or 15) is of relatively greater importance, and the first step of the reaction tends to have a more restrictive effect than the second step on the over-all rate. For this reaction there is no reason to suppose the second step would involve a change in the chromium coordination number.

In the reactions of each of the oxalato complexes with cerium(IV) it is clear that no dichromate is formed until all the oxalate has been consumed. This observation is reasonable, for while the cerium(IV)–$\mathrm{Cr(OH_2)_6^{+3}}$ reaction is moderately rapid and while dichromate ion reacts sluggishly with even free oxalic acid, chromium(IV), a probable intermediate in the cerium(IV)–chromium(III) reaction, might be expected to behave very much like cerium(IV) toward the oxalato complexes.

Our kinetic results on the three oxidations, considered alone, clearly give no information on the role of water in the mechanisms or on the geometric configurations of the activated complexes. The nonlability of many chromium(III)-oxygen bonds (*5*, *21*, *22*, *33*, *34*, *35*) together with our observations that the rates of the redox reactions are moderately large and depend on the concentrations of both cerium(IV) and chromium complexes, could suggest that the chromium would move with an unchanged primary coordination sphere into the activated complexes for the initial redox reactions. On the other hand, *cis*-$\mathrm{Cr(OH_2)_2(C_2O_4)_2^-}$ must equilibrate rapidly with smaller amounts of the trans isomer (*7*, *17*), and it may also equilibrate rapidly with very small amounts of other species, possibly including some proposed intermediates in the isomerization of *trans-* to *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ and in the racemization of the latter ion. [On the basis of theoretical estimates for activation energies for several alternative mechanisms, Hamm, Kollrack, Welch, and Perkins (*18*) have suggested a mechanism for both the isomerization and racemization processes involving a common trigonal pyramidal type intermediate of composition $Cr(OH_2)(C_2O_4)_2^-$. They do not appear to have convincingly ruled out some reasonable alternative intermediates, however, including $Cr(OH_2)_3(C_2O_4)(OC\dot{O}.CO_2)^-$ which was previously favored by Hamm (*17*) for the trans-cis isomerization.]

In the case of $Cr(C_2O_4)_3^{-3}$ it has been shown that all 12 oxygens exchange with solvent water at a rate comparable with the rate of exchange of oxygens in free oxalate (*6*, *27*) and within an order of magnitude of the racemization rate under comparable conditions. Krishnamurty and Harris (*25*) have suggested that the rapid pre-equilibrium reaction $Cr(C_2O_4)_3^{-3} + H_3O^+ \rightleftharpoons Cr(C_2O_4)_2.OC_2O_3H.H_2O^{-2}$ can accommodate the observed acid catalyses of the aquation, the racemization, and the oxygen exchange reactions of $Cr(C_2O_4)_3^{-3}$. Such proposed changes in the coordination sphere of the chromium in *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ and $Cr(C_2O_4)_3^{-3}$ would be fairly rapid, and similar changes could be involved in the formation of the activated complexes for the initial redox steps of the cerium(IV) oxidation processes. No conclusions on these details of the activated complexes can be drawn at this time.

The kinetics of the reaction of cerium(IV) with free oxalic acid in aqueous sulfuric acid have been examined by Ross and Swain (*36*) and Dodson and Black (*8*). The latter workers found the reaction to be first order in each of cerium(IV) and oxalic acid (or $HC_2O_4^-$, or $C_2O_4^{-2}$), and to have an activation energy of 16.5 kcal. per mole over the sulfuric acid concentration range 0.5 to 2.0*M*. The suggested mechanism, which would imply the reaction is first order in oxalic acid (or bioxalate) and second order in cerium(IV), must, however, be rejected. The marked increase in color which may be observed on first adding oxalic acid to solutions of cerium(IV) in sulfuric acid implies complexing between the cerium(IV) and oxalic acid. This implication together with the rate law suggests that the redox mechanism will be of similar type to that established for the manganese(III)–oxalic acid reaction (*40*, *41*). Thus, the redox reaction may well involve the rapid equilibrium formation of cerium(IV)-oxalato complexes, their rate-determining decomposition to cerium(III) and $C_2O_4^-$ (or CO_2^- and CO_2), and the rapid reaction of cerium(IV) with $C_2O_4^-$ (or CO_2^-) to produce cerium(III) and carbon dioxide. It is then likely that the cerium(IV) oxidations of free oxalate (or its conjugate acids) and of oxalate bound to chromium(III) are mechanistically similar processes.

Saffir and Taube (*37*) have found that $Co(NH_3)_5C_2O_4^+$ is smoothly oxidized by cerium(IV), with the cobalt(III) and a cerium(IV) together performing the two-equivalent oxidation of the bound oxalate. As they have observed, however, it can hardly be argued that the cobalt(III) assists in the oxidation of oxalate, since the reaction is much slower than that of cerium(IV) with free oxalate. The slower rates for the cerium(IV) oxidations of bound oxalate compared to free oxalate, as reported in the above study for $Co(NH_3)_5C_2O_4^+$, and as observed by us for $Cr(C_2O_4)_3^{-3}$, *cis*-$Cr(OH_2)_2(C_2O_4)_2^-$, and $Cr(OH_2)_4C_2O_4^+$, may be simply the result of polarizing effects of the central metal on electrons of the oxalate. The fact that chromium(III) cannot contribute to the redox process in the same way as cobalt(III), while having a vital effect on the reaction stoichiometry, probably has little or no bearing on the rates for the over-all oxidations of the chromium complexes at given levels of cerium(IV). It may in general be difficult to find examples of nonlabile oxalato complexes in which the central metal, by becoming itself reduced, can be said to contribute to the over-all rate of oxidation of bound oxalate by a one-equivalent external reagent.

For the cerium(IV)–*cis*-$Cr(OH_2)_2(C_2O_4)_2^-$ reaction the role of cerium(III) has been described here, and the role of hydrogen ion and sulfate ion will be described elsewhere (*42*). Not until similar information is obtained on the effect of cerium(III), hydrogen ion, and sulfate ion on the oxidations of $Cr(C_2O_4)_3^{-3}$ and $Cr(OH_2)_4C_2O_4^+$, will it be appropriate to discuss the relative reactivities of the three oxalato complexes toward cerium(IV).

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Literature Cited

(1) Altman, C., King, E. L., *J. Am. Chem. Soc.* **83,** 2825 (1961).
(2) Baes, C. F., *Ibid.*, **79,** 5611 (1957).
(3) Benrath, A., Ruland, K., *Z. anorg. allgem. Chem.* **114,** 267 (1920).
(4) Betts, R. H., Dainton, F. S., *J. Am. Chem. Soc.* **75,** 5721 (1953).
(5) Bjerrum, N., *Z. anorg. Chem.* **118,** 131 (1921); **119,** 39, 54, 179 (1921).
(6) Carter, J. H., thesis, Univ. of London, 1956.
(7) Cunningham, G. E., Burley, R. W., Friend, M. T., *Nature* **169,** 1103 (1952).
(8) Dodson, V. H., Black, A. H., *J. Am. Chem. Soc.* **79,** 3657 (1957).
(9) Fogel, N., Tai, J. M.-J., Yarborough, J., *Ibid.*, **84,** 1145 (1962).
(10) Fraser, R. T. M., Taube, H., *Ibid.*, **82,** 4152 (1960).
(11) Freedman, A. J., Hume, D. N., *Anal. Chem.* **22,** 932 (1950).
(12) French, D., *J. Am. Chem. Soc.* **72,** 4806 (1950).
(13) Fudge, A. J., Sykes, K. W., *J. Chem. Soc.* **1952,** 119.
(14) Furman, N. H., *J. Am. Chem. Soc.* **50,** 755 (1928).
(15) Graham, T., *Ann.* **29,** 9 (1839).
(16) Graziano, F. D., Harris, G. M., *J. Phys. Chem.* **63,** 330 (1959).
(17) Hamm, R. E., *J. Am. Chem. Soc.* **75,** 609 (1953).
(18) Hamm, R. E., Kollrack, R., Welch, G. L., Perkins, R. H., *Ibid.*, **83,** 340 (1961).
(19) Hardwick, T. J., Robertson, E., *Can. J. Chem.* **29,** 828 (1951).
(20) Haupt, G. W., *J. Res. Natl. Bur. Stds.* **48,** 414 (1952).
(21) Hunt, J. P., Plane, R. A., *J. Am. Chem. Soc.* **76,** 5960 (1954).
(22) Hunt, J. P., Taube, H., *J. Chem. Phys.* **18,** 757 (1950).
(23) King, E. L., Dismukes, E. B., *J. Am. Chem. Soc.* **74,** 1674 (1952).
(24) King, E. L., Pandow, M. L., *Ibid.*, **75,** 3063 (1953).
(25) Krishnamurty, K. V., Harris, G. M., *J. Phys. Chem.* **64,** 346 (1960); *Chem. Revs.* **61,** 213 (1961).
(26) Kukushkin, Y. N., *Zhur. Neorg. Khim.* **2,** 2371 (1957).
(27) Llewellyn, D. R., Odell, A. L., *Proc. Australian Atomic Energy Symposium* 623 (1958).
(28) Lobanov, N. I., *Zhur. Neorg. Khim.* **2,** 1035 (1957).
(29) Long, F. A., *J. Am. Chem. Soc.* **61,** 570 (1939).
(30) Medalia, A. I., Byrne, B. J., *Anal. Chem.* **23,** 453 (1951).
(31) Mendelsohn, M., Arnett, E. M., Freiser, H., *J. Phys. Chem.* **64,** 660 (1960).
(32) Palmer, W. G., "Experimental Inorganic Chemistry," p. 386, Cambridge University Press, 1954.
(33) Plane, R. A., Taube, H., *J. Phys. Chem.* **56,** 33 (1952).
(34) Postmus, C., King, E. L., *Ibid.*, **59,** 1216 (1955).
(35) Poulsen, K. G., Bjerrum, J., Poulsen, I., *Acta Chem. Scand.* **8,** 921 (1954).
(36) Ross, S. D., Swain, C. G., *J. Am. Chem. Soc.* **69,** 1325 (1947).
(37) Saffir, P., Taube, H., *Ibid.*, **82,** 13 (1960).
(38) Schug, K., Gilmore, M. D., Proceedings of Seventh International Conference on Coordination Chemistry, 1962, p. 274.
(39) Surber, H., Werner, A., *Ann.* **406,** 295 (1914).
(40) Taube, H., *J. Am. Chem. Soc.* **70,** 1216 (1948).
(41) *Ibid.*, p. 3928.
(42) Teggins, J. E., Milburn, R. M., to be published.
(43) Tong, J. Y.-P., King, E. L., *J. Am. Chem. Soc.* **82,** 3805 (1960).
(44) Vogel, A. I., "Quantitative Inorganic Analysis," 2nd ed., p. 303, Longmans, Green, London, 1951.
(45) Werner, A., *Z. anorg. Chem.* **22,** 91 (1899); *Ber.* **35,** 277 (1902); **40,** 765, 4085 (1907); *Ann.* **386,** 1 (1912); **405,** 212 (1914).

(46) Willard, H. H., Young, P., *J. Am. Chem. Soc.* **50,** 1322 (1928).
(47) *Ibid.*, **51,** 139 (1929).
(48) Yalman, R. G., *Ibid.*, **75,** 1842 (1953); **77,** 3219 (1955).

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Reactions of Some Niobium(V) and Tantalum(V) Halides with Pyridine

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The reaction of pyridine with $NbBr_5$ proceeded by oxidation-reduction to yield the niobium(IV) derivative $NbBr_4(C_5H_5N)_2$, and the oxidation products 1-(4-pyridyl) pyridinium bromide (I) and pyridinium bromide. I was identified by comparison of the ultraviolet spectra in acidic and basic solutions with those of its known salts. Reduction of $NbCl_5$ by pyridine was also observed but a different reaction stoichiometry was obtained. The reactions of $TaCl_5$ and $TaBr_5$ with pyridine afforded only the adducts $TaCl_5(C_5H_5N)$ and $TaBr_5(C_5H_5N)$. In contrast to the behavior of $NbCl_5$ and $NbBr_5$, both NbI_5 and TaI_5 dissociated in pyridine to give the adducts $MI_4(C_5H_5N)_2$, and the pyridine adduct of elemental iodine.

In previous studies (*6, 7*) of the reaction of niobium(V) chloride with ammonia and the three methylamines it was found that aminolysis was the primary mode of reaction. The extent of displacement of chloride in the reactions followed the order $NH_2Me > NH_3 = NHMe_2 > NMe_3$. While the products obtained from the reactions with NH_3, NH_2Me, and $NHMe_2$ were separated and identified, the products of the reaction with NMe_3 could not be separated. However, the over-all molar ratio of Nb:Cl:N of approximately 1:5:2 for the latter product led to the authors' suggestion that the product was a simple adduct or a mixture of tetramethylammonium chloride and tetrachloro(dimethylamido)niobium(V). The possibility of reduction was not considered.

Other work (*1*) has shown that the reaction of titanium(IV) chloride and trimethylamine yielded a mixture which was 90% tetrachloro(trimethylamine)-titanium(IV) and 10% trichlorobis(trimethylamine)titanium(III). The oxidation product of the reaction was not identified. However, the authors suggested that the oxidation products could be amine polymers or chloroamine derivatives.

Many other workers (*2, 4, 5, 15*) have reported the reduction of various metal halides with ammonia and amines, but the oxidation products of such reactions have never been positively characterized.

Generally the metal must be in the maximum valence state consistent with stability of the metal halide before reduction will take place. Where an acidic proton is available, as with primary and secondary amines, the metal-halogen bond may be broken by solvolysis of the type:

$$MX_n \cdot NHR_2 + NHR_2 = MX_{n-1} \cdot NR_2 + NH_2R_2{}^+X^- \qquad (1)$$

In the absence of an acidic proton, as with tertiary amines, the cleavage of halogen may be accomplished by a reduction of the type:

$$MX_n \cdot NR_3 + e^- = MX_{n-1} \cdot NR_3 + X^- \qquad (2)$$

Although the source of the electron is known to be the amine itself, the oxidation products of such a reaction have not been characterized.

Experimentally it has been found that primary and secondary amines react by solvolysis, while only the tertiary amines generally produce reduction, if reduction is observed. It thus seemed appropriate to study the reaction of niobium(V) halides with pyridine, where proton dissociation need not be considered and any reaction would necessarily lead to a simple adduct of pyridine or reduction of the metal halide. In this work, reduction of the niobium(V) halides was observed, and the reaction products were characterized. Elucidation of the pyridine oxidation products has permitted an interpretation of the reaction mechanism in terms of the two-electron reduction of niobium(V) by the pyridine molecule.

Experimental

Materials. Niobium metal of low oxygen content was prepared by carbon reduction of high purity niobium(V) oxide obtained from Fansteel Metallurgical Corp. The metal then was arc-melted, cut into fine turnings, and outgassed at a pressure of 8 × 10^{-5} mm. of Hg and a temperature of 2050° for 2 hours.

ANALYSIS. Found: O, 35 p.p.m.; N, 575 p.p.m.; C, 3500 p.p.m.

Tantalum metal was obtained from the National Research Corp. as a granular powder of low oxygen content and a stated purity of 99.9+ %.

Chlorine was distilled from cylinders directly into a side arm of the reaction tubes for halide preparations, using a dry ice–acetone bath. After distillation the liquid was frozen in liquid nitrogen and outgassed under high vacuum.

Reagent-grade bromine was dried over phosphorus(V) oxide and distilled into dry, evacuated flasks. Samples then were vacuum-distilled into reaction tubes for the halide preparations.

Reagent-grade iodine was transferred directly to the reaction tubes for halide preparations and was outgassed thoroughly at room temperature under high vacuum.

Pyridinium halides were prepared by bubbling anhydrous hydrogen halide gas through a solution of pyridine in anhydrous ethyl ether. The precipitates then were filtered, washed with ethyl ether, and dried under high vacuum at room temperature.

1-(4-Pyridyl)pyridinium dichloride was obtained from Eastman Organic Chemicals. It was purified by dissolving the solid in concentrated hydrochloric acid, boiling the solution with activated charcoal, evaporating to a small volume, and stirring into absolute ethanol. The pure white crystalline product was then dried under high vacuum at room temperature.

ANALYSIS. Calcd. for $C_{10}H_{10}N_2Cl_2$: Cl, 30.94. Found: Cl, 30.43.

1-(4-Pyridyl)pyridinium dibromide was prepared by dissolving 1-(4-pyridyl)-pyridinium dichloride in concentrated hydrobromic acid and evaporating nearly to dryness three times with concentrated hydrobromic acid. The solution then was stirred into cold absolute ethanol. The pale yellow precipitate which formed was filtered and dried under high vacuum at room temperature.

Analysis. Calcd. for $C_{10}H_{10}N_2Br_2$: Br, 50.20. Found: Br, 49.97.

Spectro-grade pyridine was dried over calcium hydride, thoroughly outgassed on the vacuum line, distilled onto fresh barium oxide, and again outgassed. The liquid was finally distilled into a clean, dry, evacuated flask from which the samples for investigation were distilled.

Reagent-grade chloroform was distilled through a 30-plate, fractional distillation column at a reflux ratio of 10 to 1 and collected over outgassed calcium hydride. The purified solvent then was frozen in liquid nitrogen and outgassed under high vacuum while it warmed slowly to room temperature.

Spectro-grade acetonitrile was distilled through a 30-plate, fractional distillation column at a reflux ratio of 10 to 1 and collected over thoroughly outgassed Molecular Sieves. The purified solvent was frozen in liquid nitrogen and outgassed under high vacuum as it warmed slowly to room temperature.

Spectra. The visible and ultraviolet spectra for various solutions were determined using a Cary 14 recording spectrophotometer and 1-cm. quartz cells. Infrared spectra were obtained using a Perkin-Elmer 13 infrared spectrophotometer with sodium chloride optics and cells.

X-Ray Powder Patterns. Samples for x-ray pattern determinations were sealed in 0.2-mm. glass capillary tubes under an atmosphere of argon. The samples were then exposed to nickel-filtered, Cu*Kα* radiation in an 11.459-cm. Debye-Scherrer camera for 18 to 20 hours.

Preparation of Niobium(V) and Tantalum(V) Halides. The niobium(V) and tantalum(V) chloride and bromide were prepared in a system of sealed, evacuated bulbs by reacting the pure metal with gaseous halogen. For the chlorides the metal was maintained at 300° to 350° under a chlorine pressure of approximately 70 mm. of Hg; the chlorine pressure was maintained by keeping the liquid chlorine immersed in a dry ice–acetone bath. For the bromides the metal was maintained at a temperature of 400° to 450° under a bromine pressure of approximately 250 mm. of Hg, maintained by leaving the liquid bromine at room temperature.

When the reactions were complete, excess halogen was isolated by freezing it in liquid nitrogen. The pure product was then separated from the system in a sealed bulb, which was left unopened until the product was needed.

The niobium(V) and tantalum(V) iodides were prepared by the method reported by Corbett and Seabaugh for niobium(V) iodide (3).

Analytical data for the pentahalides are given in Table I.

Table I. Analytical Data for MX_5

	Calcd.		*Found*	
Compound	*%M*	*%X*	*%M*	*%X*
$NbCl_5$	34.39	65.61	34.49	65.37
$NbBr_5$	18.85	81.14	18.59	79.81
NbI_5	12.77	87.23	12.77	87.20
$TaCl_5$	50.53	49.47	50.40	49.35
$TaBr_5$	31.16	68.84	31.10	68.00
TaI_5	22.10	77.90	22.30	77.60

Reactions with Pyridine. The reaction products of niobium(V) and tantalum(V) halides with pyridine were prepared in a sealed, evacuated flask which contained a stirring bar and was designed for easy weighing on the balance. The flask was first evacuated and weighed. A sample of metal halide was transferred to the flask in the glove box, and the flask was again evacuated and weighed to obtain the weight of sample.

Approximately 30 ml. of anhydrous pyridine were condensed on the sample of metal halide and the mixture was stirred at room temperature until the reaction was complete. The reactions were considered complete when no unreacted metal halide could be observed visually. Reactions where the reagents were stirred over a much longer period of time (2 to 3 days) gave results entirely in agreement with those obtained for the shorter reaction time.

Excess pyridine was distilled from the flask, and the resulting product was dried under high vacuum at room temperature to a constant weight. The amount of pyridine utilized in the reaction could then be determined by weight difference before and after reaction. Complete analytical results for the crude products obtained with the chlorides and bromides are given in Table II. Because the tantalum(V) and niobium(V) iodides both yielded free iodine in the reaction with pyridine, their products were washed with chloroform, as described later, before analysis.

Table II. Analytical Data for Products of Reaction of Niobium(V) and Tantalum(V) Chlorides and Bromides with Pyridine

Reactants	*Calcd. for $MX_5 \cdot py$*			*Found*			*Ratios*	
	% M	*% X*	*% py*	*% M*	*% X*	*% py*	*Py/M*	*X/M*
$NbCl_5 \cdot py$	...	...	...	36.86 to 38.52	19.81 to 20.72	44.33[a] to 40.76	2.39 to 2.63	4.98 to 4.87
$NbBr_5 \cdot py$	...	...	...	12.46 to 12.49	52.67 to 52.96	34.87[a] to 34.55	3.37 to 3.46	4.96 to 4.93
$TaCl_5 \cdot py$	40.55	41.40	18.08	40.26	41.05	17.80	0.99	5.01
$TaBr_5 \cdot py$	60.60	27.41	11.98	60.30	27.10	11.82	1.00	5.04

[a] Determined by difference.

Washing Procedures. The metal halide–pyridine reaction mixtures were washed in a sealed apparatus designed for continuous extraction in vacuo. Samples were transferred to and from the apparatus in a glove box under an atmosphere of argon. Washings were considered to be complete when the filtrate coming through the filter became colorless.

Oxidation-Reduction Titrations. The extent of reduction resulting from reaction of niobium(V) chloride and bromide with pyridine was determined by indirect titration of crude reaction mixtures with standard ammonium tetrasulfatocerate(IV) solution. Samples were stirred overnight in a stoppered flask with an excess of iron(III) ammonium sulfate. Any iron(II) formed by reaction with the niobium complex mixture was then titrated with the standard tetrasulfatocerate(IV) solution using ferroin as indicator. Results of these determinations are given in Table III.

Table III. Results of Oxidation-Reduction Titrations

Sample	*Solvent*	*Titrant*	*Pyridine/ Metal for Sample*	*% Reduction*
$NbCl_5$-pyridine reaction product	1*N* H_2SO_4 excess Fe^{+3}	Ce^{+4} in 1*N* H_2SO_4	2.63	64.7
			2.63	62.9
			2.53	66.1
			2.53	70.5
$NbBr_5$-pyridine reaction product	1*N* H_2SO_4 excess Fe^{+3}	Ce^{+4} in 1*N* H_2SO_4	3.44	88.1
			3.44	89.5

Degradation of 1-(4-Pyridyl)pyridinium Ion. Samples of 1-(4-pyridyl)-pyridinium dichloride and dibromide dissolved in dilute hydrochloric acid were treated with concentrated sodium hydroxide solution until strongly basic. The solutions turned a bright yellow color and gave the absorption spectrum shown as A in Figure 1. The broad peak was centered at approximately 432 mμ, with the sharper peak centered at 365 mμ. The yellow solutions were then heated near the boiling point. The spectrum obtained after heating the basic solution is shown as B in Figure 1. The broad peak at 432 mμ had disappeared, while the peak at 365 mμ had sharpened and intensified.

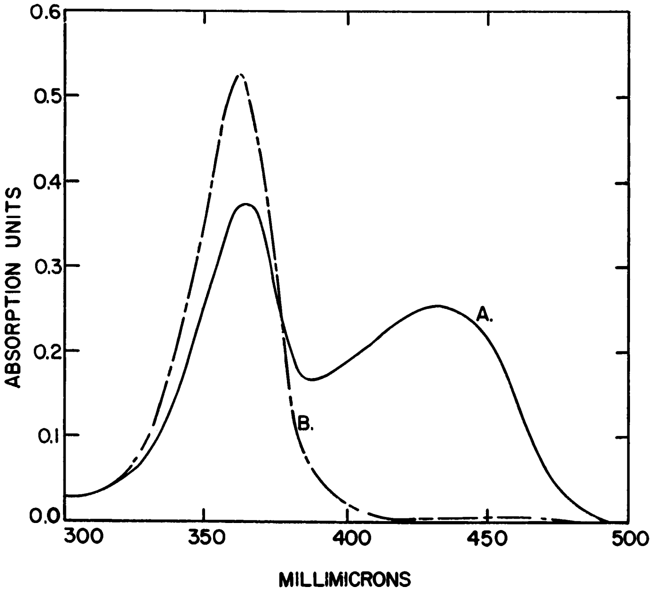


Figure 1. Absorption spectra produced by degradation of 1-(4-pyridyl)pyridinium ion in basic solution

A. Immediately following addition of NaOH
B. After heating at 100°

When a sample of the niobium(V) chloride–pyridine or niobium(V) bromide–pyridine reaction mixture was dissolved in dilute acid, filtered to remove precipitated niobium oxides, and treated with concentrated sodium hydroxide solution, the same set of spectra were observed for the resulting solution as for the 1-(4-pyridyl)pyridinium dihalides. The spectra before and after heating the solutions from the reaction mixtures are shown in Figure 2. Here also the peaks occurred at 432 and 365 mμ, with the 432-mμ peak absent after heating.

Separation of 1-(4-Pyridyl)pyridinium Ion with Tetraphenylborate(III) Ion. Samples of the niobium(V) chloride or niobium(V) bromide–pyridine reaction mixtures were hydrolyzed in concentrated hydrochloric acid. Aliquots were diluted and neutralized with sodium carbonate to a pH of approximately 8. Sodium tetraphenylborate(III) solution then was added and a precipitate of 1-(4-pyridyl)pyridinium tetraphenylborate(III) was produced. The precipitate was filtered and extracted with concentrated hydrochloric acid. The ultraviolet absorption spectrum of the extract is shown in Figure 3 for comparison with the spectrum of a known sample of 1-(4-pyridyl)pyridinium dichloride in dilute hydrochloric acid.

Preparation of Dianiline Derivative of Glutaconaldehyde. A sample of the niobium(V) chloride–pyridine reaction mixture was hydrolyzed in dilute aqueous ammonia, and the solution was filtered to remove precipitated niobium(V) oxide.

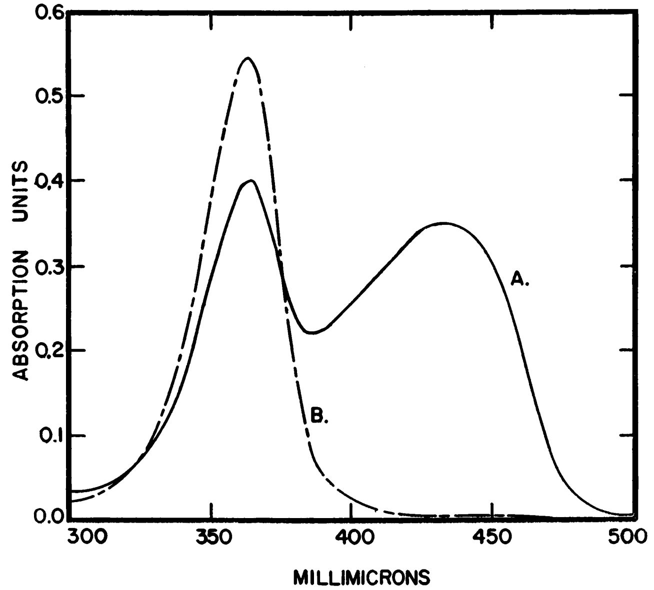


Figure 2. Absorption spectra of solution produced by hydrolysis of $NbBr_5$-pyridine reaction mixture

A. Immediately following addition of NaOH
B. After heating at 100°

It then was treated with concentrated sodium hydroxide solution and boiled to convert all 1-(4-pyridyl)pyridinium ion to the sodium salt of glutaconaldehyde. The resulting solution was acidified with hydrochloric acid and treated with excess aniline. On heating to boiling the dark red dianiline derivative of glutaconaldehyde precipitated and was filtered off. This precipitate was then recrystallized twice from absolute ethanol. The melting point of this precipitate (174°–177°) corresponded closely to that given for the dianiline derivative of glutaconaldehyde (178°) (*13*).

Results and Discussion

Reactions of Tantalum(V) Chloride and Bromide with Pyridine. Table IV summarizes the reactions of niobium(V) and tantalum(V) halides with pyridine. In contrast to the niobium(V) halides, the reactions of these tantalum halides and pyridine were rapid and complete within a few minutes, and gave no evidence of reduction of the tantalum.

Table IV. Reactions of Niobium and Tantalum Pentahalides with Pyridine at Room Temperature

Metal Halide	*Pyridine/Metal, Weight Gain*	*Product Color*	*Required Reaction Time*
$NbCl_5$	2.39–2.63	Brown	24–48 hr.
$NbBr_5$	3.37–3.46	Green	12–24 hr.
$TaCl_5$	0.99[a]	White	~Minutes
$TaBr_5$	1.02	Yellow	~Minutes
NbI_5	Volatile product[b]	Black	—
TaI_5	Volatile product[b]	Brick red	—

[a] From direct analysis.
[b] Loss of iodine.

Both the weight gain data from the reactions and the analyses of the products clearly showed that only the 1 to 1 adducts, $TaCl_5 \cdot py$ and $TaBr_5 \cdot py$, were formed. These reactions gave no evidence of formation of a 2 to 1 adduct such as that reported by Lindner and Feit (*11*) for tantalum(V) chloride and pyridine—i.e., $TaCl_5 \cdot 2py$. Thus it does not appear that tantalum may expand its coordination number beyond 6 in these compounds. The solids are hydrolyzed only slowly in water, which wets the surface of the solids with difficulty.

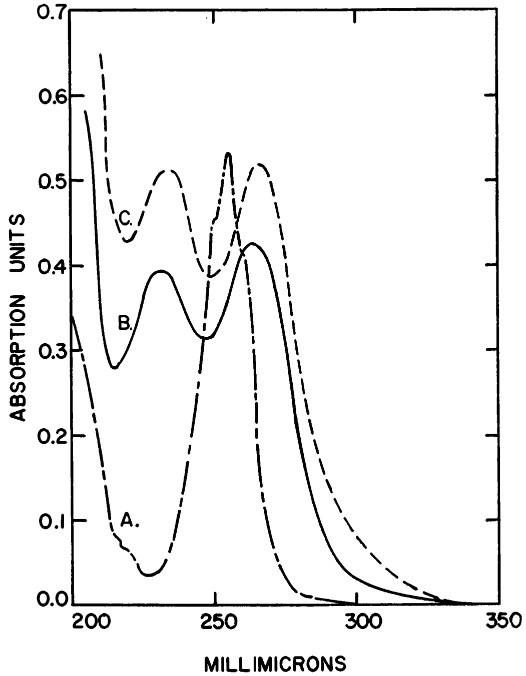


Figure 3. Absorption spectra

A. Pyridinium halide
B. 1-(4-Pyridyl)pyridinium dihalide
C. Solution obtained by tetraphenylborate separation of 1-(4-pyridyl)pyridinium ion

Reactions of Niobium(V) Chloride and Bromide with Pyridine. These reactions proceeded with an initial, rapid formation of a voluminous white solid in the case of the chloride and a maroon red solid in the case of the bromide, followed by a much slower reaction in each case. The solution and solid both became brown in the chloride reaction, while a bulky green solid separated from the red solution of the bromide. When the reaction was complete in the latter case, the solution above the green solid was almost colorless.

Weight gain data and oxidation-reduction titers (Table II) for the niobium(V) chloride and bromide reaction products both indicated the reduction of niobium(V) to niobium(IV). The niobium(IV) adducts were separated by washing the crude reaction mixtures with anhydrous acetonitrile. This solvent removed the various organic products of the initial reaction plus any unreduced niobium compounds. Analysis of the washed products gave ratios of Nb:X:py of 1:4:2 and agreed with analyses for samples of $NbCl_4 \cdot py_2$ and $NbBr_4 \cdot py_2$ which were prepared by reaction of niobium(IV) chloride and bromide with pyridine (*12*).

ANALYSIS. Calcd. for $NbCl_4 \cdot py_2$: Nb, 23.70; Cl, 36.20; py, 40 40. Found: Nb, 23.4; Cl, 36.7, py, 38.1; py/Nb, 1.92. Calcd. for $NbBr_4 \cdot py_2$: Nb, 16.30; Br, 56.00; py, 27.70. Found: Nb, 16.5; Br, 56.5; py, 27.0; py/Nb, 1.92.

A further identification of the niobium(IV) halide–pyridine complexes was provided by x-ray powder pattern data, as shown in Table V. The values obtained from these measurements corresponded closely to those found for $NbBr_4 \cdot py_2$ and $NbCl_4 \cdot py_2$ (*12*).

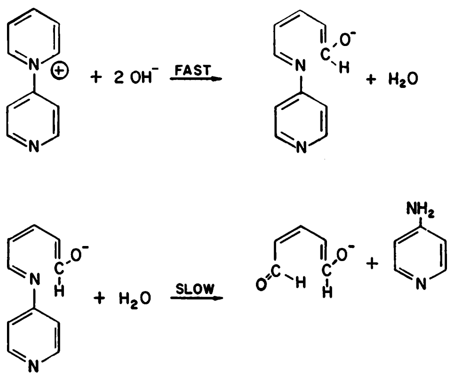
Table V. Most Intense Powder Pattern Lines[a] in Metal Halide–Pyridine Reaction Products

$NbCl_4 \cdot py_2$				$NbBr_4 \cdot py_2$				$NbI_4 \cdot py_2$ from NbI_4		$TaI_4 \cdot py_2$ from TaI_5	
From $NbCl_4$		From $NbCl_5$		From $NbBr_4$		From $NbBr_5$					
d, A.	R.I.	d, A.	R.I.	d, A.	R.I.	d, A.	R.I.	d, A.	R.I.	d, A.	R.I.
6.50	10	6.46	10	6.62	10	8.60	8	6.76	10	6.77	10
6.12	10	6.09	9	5.30	6	6.60	10	3.94	10	3.95	10
5.16	9	5.18	7	3.88	9	3.88	9	3.85	10	3.84	7
4.15	7	3.83	8[b]	3.69	7	3.28	8	3.47	10	3.45	8
3.83	10	3.18	8	3.27	8	3.25	8	2.79	10	2.78	10
3.16	8	2.58	8[b]	2.64	9	2.65	10[b]	2.57	8	2.56	6
2.58	9	2.51	7	2.53	7	2.49	6[b]	2.15	6		
2.50	9			2.42	6	2.41	8	1.98	6		

[a] Intensities estimated visually relative to a value of 10 for most intense line.
[b] Also observed in powder pattern of respective pyridinium halide.

It was thus shown that the tetrahalodi(pyridine)niobium(IV) complexes were the reduction products of the reactions of niobium(V) chloride and niobium(V) bromide with pyridine.

The characteristic spectra obtained by degradation of 1-(4-pyridyl)pyridinium ion in strongly basic solution, discussed earlier and illustrated in Figure 1, led to the identification of this ion as the major oxidation product of the reactions. The initial step in the degradation is a ring opening reaction (*9*) initiated by attack of OH^-. This reaction yields a 4-aminopyridine derivative of glutaconaldehyde, which is believed to be the source of the absorption band found at 432 mμ. Heating near the boiling point then produces hydrolysis to yield 4-aminopyridine and the sodium salt of glutaconaldehyde. The latter is believed to be responsible for the absorption band observed at 365 mμ. The degradation thus is considered to proceed as follows:



The presence of 1-(4-pyridyl)pyridinium ion in the crude reaction mixtures was detected by the observation of this same set of spectra in solutions prepared by hydrolysis of the reaction mixtures in acid solution, followed by treatment with strong base and heating (Figure 2).

Further evidence for the presence of 1-(4-pyridyl)pyridinium ion in the reaction mixtures was provided by a separation technique based on the precipitation of the 1-(4-pyridyl)pyridinium ion in the presence of pyridine with Ph_4B^- in a solution with a pH of 8. This procedure was necessary, since the ultraviolet spectrum of 1-(4-pyridyl)pyridinium ion in a solution prepared by acid hydrolysis of the crude reaction products was completely obscured by the intense spectrum of pyridinium ion, which also was formed by the hydrolysis of the reaction products. However, as shown in Figure 3, the 1-(4-pyridyl)pyridinium ion was easily identified after its separation as the tetraphenylborate(III) salt.

Finally, the oxidation product was positively identified by preparation of a known derivative of the glutaconaldehyde obtained by basic degradation of the 1-(4-pyridyl)pyridinium ion present in a sample of the chloride reaction mixture.

These three procedures left little doubt that 1-(4-pyridyl)pyridinium ion was the major oxidized product of the reaction of niobium(V) bromide and chloride with pyridine.

Samples of both the bromide and chloride crude reaction mixtures were extracted with anhydrous chloroform to obtain a chloroform-soluble residue. Chloroform extraction was chosen here, because the niobium(IV) adducts appeared to be substantially insoluble in this solvent. Samples of the soluble residue were dissolved in anhydrous chloroform for infrared analysis. The resulting absorption spectra were then compared to those obtained in the same way for known samples of pyridinium chloride and bromide (Table VI).

Table VI. Infrared Absorption Bands for Pyridinium Bromide and Soluble Residue from $CHCl_3$ Washing of $NbBr_5$-Pyridine Reaction Product

Pyridinium Bromide		*Soluble Residue*	
Frequency, cm.$^{-1}$	*R.I.*[a]	*Frequency, cm.$^{-1}$*	*R.I.*[a]
2975	S	2975	S
2300–2800	V.S. (broad)	2300–2800	V.S. (broad)
2050	S	2050	S
1945	M	1945	M
1840	W	1840	W
1630	M	1630	M
1610	S	1610	S
1535	M	1530	M
1486	S	1490	S
1388	M		
1336	M	1335	M
1243	M		
1218	M		
1164	W	1162	M

[a] V.S. = very strong; S = strong; M = medium; W = weak.

The spectrum obtained for the soluble residue from the chloride mixture gave no evidence of the presence of pyridinium chloride. However, the residue from the bromide mixture gave an infrared absorption spectrum containing 11 of the 14 bands observed in the known sample of pyridinium bromide, including a characteristic, very broad band between 2300 and 2800 cm.$^{-1}$ Thus there was evidence that pyridinium bromide was a constituent of the reaction mixture obtained with niobium(V) bromide, but that pyridinium chloride was not present in any significant amounts in the chloride reaction mixtures.

From these observations it was concluded that the major products of the reduction of niobium(V) chloride with anhydrous pyridine were tetrachlorodi(pyridine)niobium(IV) and 1-(4-pyridyl)pyridinium dichloride. Oxidation-reduction titrations indicated that this reduction accounted for approximately 70% of the reaction products. In view of the rapid reaction of tantalum(V) halides with pyridine to form 1 to 1 adducts, it was assumed that the remaining 30% of niobium(V) which was not reduced was present in the reaction mixture as pentachloro(pyridine)niobium(V). On this basis the following over-all reaction is proposed:

$$\begin{aligned} &70\% \quad 2NbCl_5 + 6py = 2NbCl_4 \cdot py_2 + (py)_2H^{+2}Cl_2^{-2} && (3) \\ &30\% \quad NbCl_5 + py = NbCl_5 \cdot py \end{aligned}$$

An over-all molar ratio of 2.40 pyridines per niobium in the reaction mixture is given by these equations. This agrees well with the ratio of 2.39 to 2.63 observed from weight gain data.

Similarly, it was concluded that in the reduction reaction of niobium(V) bromide with pyridine the major products were tetrabromodi(pyridine)niobium(IV), pyridinium bromide, and 1-(4-pyridyl)pyridinium bromide. Oxidation-reduction titrations indicated approximately 90% reduction. The remaining 10% of niobium was assumed to be present as pentabromo(pyridine)niobium(V). The over-all reaction was indicated to be:

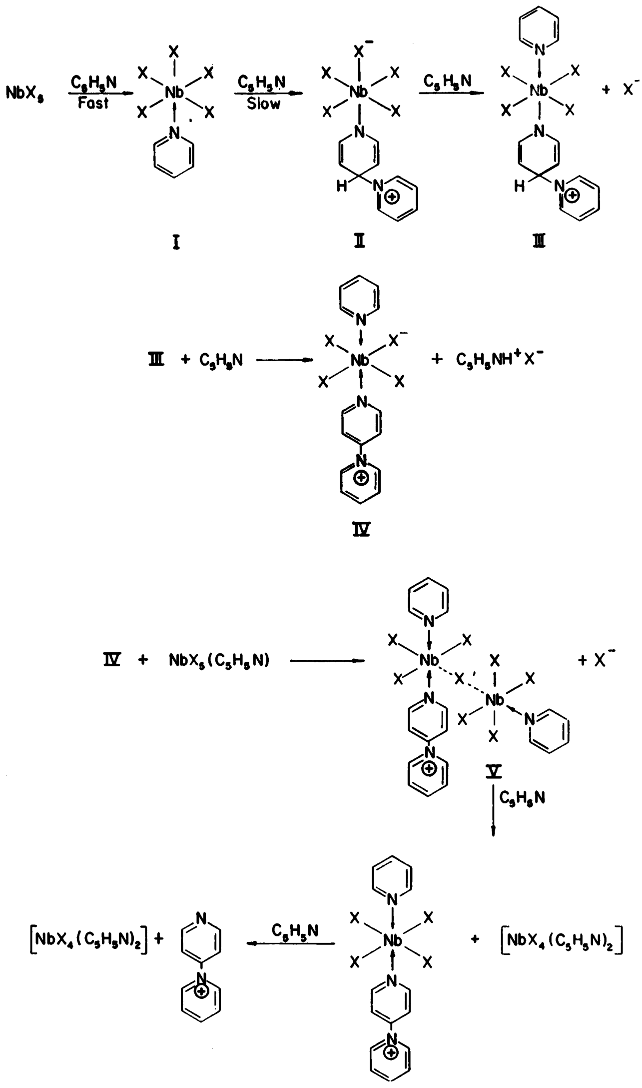
$$\begin{aligned} &90\% \quad 2NbBr_5 + 7py = 2NbBr_4 \cdot py_2 + pyH^+Br^- + (py)_2{}^+Br^- && (4) \\ &10\% \quad NbBr_5 + py = NbBr_5 \cdot py \end{aligned}$$

Calculations based on these equations yielded an over-all molar ratio for the reaction mixture of 3.25 pyridines per niobium; values of 3.37 to 3.42 were obtained from weight gain data.

It was necessary to assume that 1-(4-pyridyl)pyridinium dichloride was formed without the formation of pyridinium chloride in the chloride reaction mixture, in order to account for the stoichiometries observed. The absence of the characteristic spectra of pyridinium chloride from samples of chloroform-soluble residues supported this assumption. However, for similar reasons it was necessary to conclude that pyridinium bromide was a product of the bromide reaction. The difference between the two reactions in this respect may be explained by the relative solubilities of the two halide salts of the protonated 1-(4-pyridyl)pyridinium ion in pyridine. This point, however, was not pursued further in this investigation.

Proposed Mechanisms for Reduction Reactions. Any mechanism proposed for the reduction of niobium(V) halides with pyridine must incorporate the necessary two-electron oxidation-reduction step required for the oxidation of pyridine to 1-(4-pyridyl)pyridinium ion. In view of the known acid properties of the niobium(V) halides and the rapid reaction of the tantalum(V) halides to give 1 to 1 pyridine adducts, the mechanism must also include the initial coordination of pyridine to the niobium(V) halide. The reduction might then proceed through the steps shown opposite.

The existence of a substituted pyridine molecule such as III was considered as a probable intermediate for the oxidation of pyridine to 1-(4-pyridyl)pyridinium ion by thionyl chloride (*10*). The authors believe the mechanism of the reaction with thionyl chloride to be similar to that proposed here, but further discussion of this point must await knowledge about the fate of the thionyl chloride, which has not been elucidated. More recently, an intermediate such as II or III was proposed to account for the facile bromination of pyridine in the presence of thionyl chloride (8).



The formation of a bridged, activated intermediate such as V is a well known hypothesis for explanation of many electron exchange and oxidation-reduction reactions (*14*). The two-electron reduction of niobium by pyridine makes this step necessary, since niobium(III) must be formed only as an intermediate. No evidence was found for the presence of niobium(III) in the final products. If such an intermediate is involved, it would seem likely that the reduction of tantalum(V) to tantalum(IV) should be observed when a mixture of tantalum(V) and niobium(V) halides reacts with pyridine. Studies of such mixtures, now in progress, indicate an extent of reduction in excess of that expected for niobium (V) halide alone. It is thus possible that an intermediate analogous to V could be producing a small amount of reduction of tantalum(V) in such mixtures.

The last step in the proposed mechanism, which shows the displacement of coordinated 1-(4-pyridyl)pyridinium ion, is required, since only the tetrahalodi(pyridine) adducts were found in the reaction mixtures. The acetonitrile extractions also demonstrated that the 1-(4-pyridyl)pyridinium ion could be easily washed from the reaction mixtures, and indicated the presence of this ion as a free halide rather than as a constituent of the complex.

Reactions of Tantalum(V) and Niobium(V) Iodides with Pyridine. Both niobium(V) and tantalum(V) iodide were reduced in pyridine. In each case the di-adduct of pyridine with the metal tetraiodide was produced, along with elemental iodine as its pyridine complex. The two reduction products were identified by analysis after washing with chloroform to remove the iodine liberated in the reaction. Further identification of the tantalum product was provided by x-ray diffraction data, which compared favorably to those obtained for samples of the tetraiododi(pyridine)niobium(IV) as shown in Table V.

ANALYSIS. Calcd. for $NbI_4 \cdot py_2$: Nb, 12.2; I, 66.9; py,, 20.9. Found: Nb, 12.0; I, 67.6; py (by difference), 20.4; py/Nb, 1.98. Calcd. for $TaI_4 \cdot py_2$: Ta, 21.4; I, 60.0; py, 18.6. Found: Ta, 21.3; I, 61.4; py, 12.5; py/Ta, 1.34.

The iodine was removed from the reaction mixtures by vacuum sublimation and subsequently identified by its characteristic spectrum in pyridine solution. A solution of the sublimate from these reaction products gave an absorption maximum at 369 mμ, while a solution prepared by dissolving elemental iodine in pyridine produced an absorption band of similar shape with a maximum at 370 mμ.

Thus it was shown that while the iodides were reduced, the reactions followed an entirely different path than those of the chlorides and bromides. These reactions may be described by Equation 5. However, the reactions may proceed through initial coordination of pyridine (Equation 6), followed by dissociation to yield the final products (Equation 7).

$$2MI_5 + 5py = 2MI_4 \cdot py_2 + pyI_2 \quad (5)$$

$$MI_5 + py = MI_5 \cdot py \quad (6)$$

$$2MI_5 \cdot py + 3py = 2MI_4 \cdot py_2 + pyI_2 \quad (7)$$

This mode of reaction for the iodides is consistent with the lower stability of the pentaiodides. For example, it has been shown that niobium(IV) iodide can be prepared by dissociation at temperatures as low as 270° (Equation 8).

$$MI_5(s) = MI_4(s) + {}^1/_2I_2(g) \quad (8)$$

Apparently the dissociation is enhanced in pyridine, owing to formation of the stable complexes of both niobium(IV) iodide and elemental iodine. Although some reduction of tantalum(V) iodide also occurred in pyridine, the analytical data suggest that this reaction was not complete, and that some unreduced tantalum(V) iodide remained in the washed product. By comparison with niobium (V) iodide, the smaller extent of reduction of tantalum(V) iodide may be accounted for in terms of the greater stability of the latter toward the dissociation shown in Equation 8.

Literature Cited

(1) Antler, M., Laubengayer, A. W., *J. Am. Chem. Soc.* 77, 5250 (1955).
(2) Cavell, R. G., Clark, H. C., *J. Inorg. Nucl. Chem.* 17, 257 (1961).

(3) Corbett, J. D., Seabaugh, P., *Ibid.*, **6**, 207 (1958).
(4) Fowles, G. W. A., McGregor, W. R., *J. Chem. Soc.* **1958**, 136.
(5) Fowles, G. W. A., Pleass, C. M., *Ibid.*, **1957**, 1674.
(6) *Ibid.*, p. 2078.
(7) Fowles, G. W. A., Pollard, F. H., *Ibid.*, **1952**, 4938.
(8) Garcia, E. E., Greco, C. V., Hunsberger, I. M., *J. Am. Chem. Soc.* **82**, 4430 (1960).
(9) Klingsberg, E., ed., "Pyridine and Its Derivatives. I," pp. 57–61, Interscience, New York, 1960.
(10) Koenigs, E., Greiner, H., *Ber.* **64**, 1049 (1931).
(11) Lindner, K., Feit, H., *Z. anorg. u. allgem., Chem.* **132**, 10, (1924).
(12) McCarley, R. E., Torp, B. A., *Inorg. Chem.*, in press.
(13) Schöpf, C., Hartmann, A., Koch, K., *Ber.* **69B**, 2766 (1936).
(14) Taube, H., *Inorg. Chem. Radiochem.* **1**, 1–53, (1959).
(15) Wardlow, W., Webb, H. W., *J. Chem. Soc.* **1930**, 2100.

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