CATALYTIC EFFECTS OF METAL CHELATE COMPOUNDS

ARTHUR E. MARTELL

Department of Chemistry, Texas A & M University, College Station, Texas, U.S.A.

INTRODUCTION

This paper is essentially a progress report on the developments in the field of metal chelate catalysis since the first review of this subject fifteen years ago[1]. For the purpose of defining the scope of this field, metal chelate catalysis is considered to include any reaction that is altered or modified by metal ions through chelate ring formation, as well as reactions of metal chelates themselves. The relatively narrow definition of catalysis, in which the catalytic substance remains unaltered at the end of each reaction cycle or sequence thus constitutes only a part of the overall topic under discussion. The catalytic reactions which do not fit this specific definition may be considered as being "promoted" or "inhibited" by metal chelate ring formation.

CLASSIFICATION OF REACTION TYPES

Since the central idea behind this review is "metal chelate catalysis", the reactions to be discussed are classified in terms of what happens to the chelate ring. Thus the following types of reactions may be considered:

I. Reactions in which metal chelate rings are formed
   (a) Template synthesis of macrocyclic rings
   (b) Nucleophilic reactions
      1. Solvolysis
      2. Transphosphorylation
      3. Schiff base formation
      4. Stereospecific polymerization
   (c) Electrophilic substitution
      1. Carboxylation
      2. Acylation
   (d) Molecular rearrangements
   (e) Chelate ligand displacement reactions
   (f) Decarboxylation

II. Reactions in which the metal chelate ring is altered (substitution, elimination, and rearrangement reactions)
   (a) Nucleophilic substitution
   (b) Electrophilic substitution
   (c) Elimination and isomerization reactions

III. Reactions in which metal chelate rings are broken
   (a) Direct oxidation of the ligand by the metal ion
      1. Metal ion as oxidant
      2. Metal ion catalysis

(b) Mixed ligand complex formation with oxidant
(c) Rearrangements and internal redox reactions of the ligand

IV. Reactions in which the metal chelate ring is not altered
(a) Masking of reactivity (reactions of remote groups)
(b) Chelate ring functions as a carrier of the metal ion
1. Solvolysis by partially-chelated metal ions
2. Redox catalysis
(c) Complex systems in which the metal chelate is regenerated.

There are many other ways of classifying reactions of metal chelate compounds. Thus reaction types such as substitution (electrophilic and nucleophilic), isomerization, redox reactions, chelate formation (association) and dissociation reactions may be employed. Most of these classifications are involved as sub-topics of the general classifications given above. From a mechanistic point of view, metal ions may be considered to have the following effects on a coordinated ligand:

1. *Electronic.* Electrons are shifted toward the metal ion, either partially in ionic reactions, or completely in redox reactions. This effect favours nucleophilic substitution or, by first eliminating a positive group, may facilitate electrophilic substitution.

2. *Steric.* The metal ion will generally impose steric requirements on ligand reactions due to metal chelate ring formation, and to the geometry of the "coordination sphere" of the metal ion.

3. *Equilibrium.* The formation of a metal chelate compound is favoured by strong entropy effects in dilute solution, thus increasing the probability of forming a reactive species, or increasing the probability of forming an activated complex containing metal chelate rings.

All of these factors are also important when a catalytic, partially chelated, metal ion combines with a reactive secondary ligand.

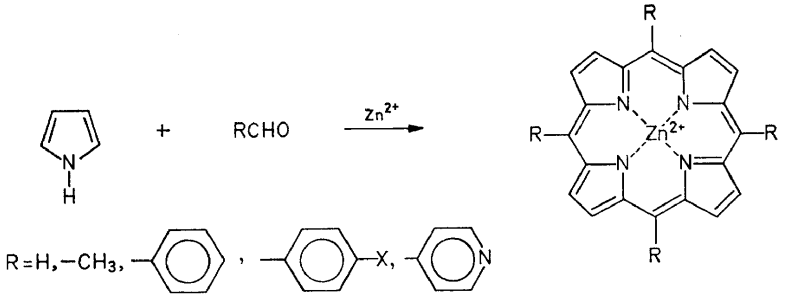
I. REACTIONS IN WHICH METAL CHELATE RINGS ARE FORMED

(a) Template synthesis of macrocyclic rings

The terms "template hypothesis" and "template synthesis" have been suggested[2] for reactions in which the central metal ion serves as a "template" on which to position ligands which then react so as to form metal chelate rings about the metal ion. When this process continues so as to surround the metal with a fused cyclic ring system, a "macrocyclic" ring is said to be formed[2].

Although the synthesis of phthalocyanines from phthalonitrile and transition metal salts has been known for a long time[3], the first reported description of the template action of a metal ion in producing a macrocyclic metal chelate ring system is the use of Zn^{2+} ion for improving the yield of tetraphenylporphine, and other *meso*-tetrasubstituted porphines (*Figure 1*)[1,4]. These reactions have been extended to the synthesis of many derivatives of tetrasubstituted metal porphines[5–8]. Although the metal ion improves the yields

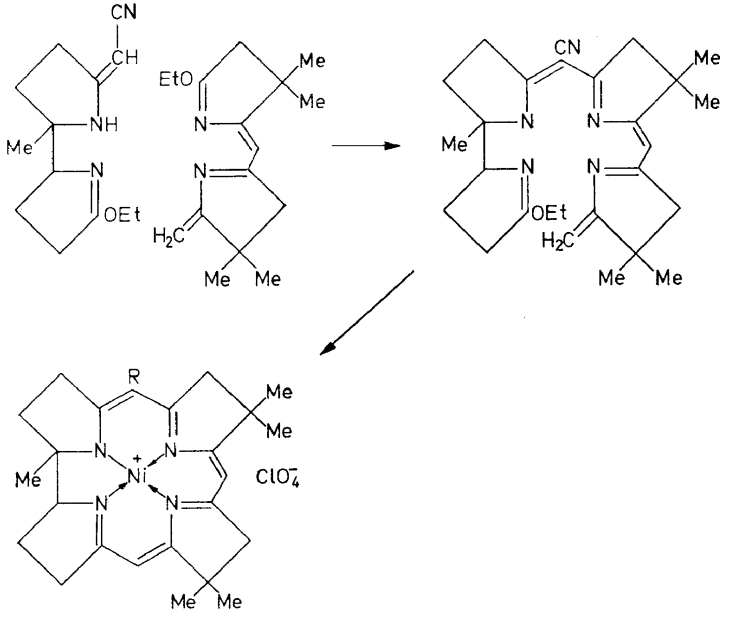
of these reactions by as much as a factor of ten, the best yields achieved thus far are still low (about 10 per cent), probably because of the fact that four monodentate ligands must be brought together in a one-step synthesis.



Calvin *et al.*, 1943, 1946
Priesthoff and Banks, 1954
Thomas and Martell, 1956
Fleischer, 1962
Badger *et al.*, 1964

Figure 1. Template synthesis of macrocyclic rings: Direct porphine synthesis

Recently Cu(II) and Ni(II) salts have been used almost routinely to improve yields in the synthesis of substituted porphyrins, chlorins, corrins, and related substances. An example of the synthesis of a corrin using the template action of Ni(II) described by Eschenmoser[9] is given in *Figure 2*. An extensive review of the synthesis of porphines and related compounds has



(Eschenmoser, 1963)

Figure 2. Total synthesis of a corrin

recently been published[10]. The stepwise template synthesis of nickel(II) phthalocyanine (*Figure 3*) has been described recently by Hurley *et al.*[11]. The yields in these reactions are relatively high (50–90 per cent), as might be expected from the fact that each step involves the bringing together of only two reacting ligands around the metal ion, or the simple closing of a ring between ligands that are already coordinated and positioned by the metal ion.

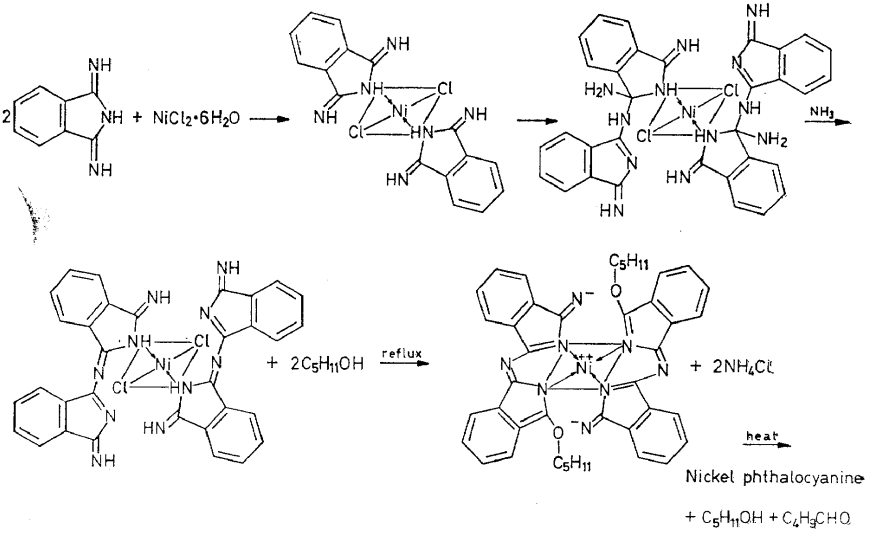
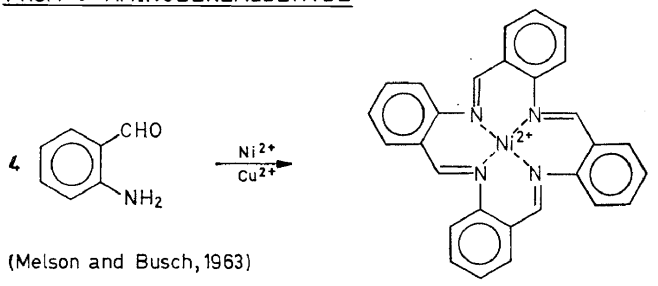


Figure 3. Stepwise formation of nickel phthalocyanine

High yields in the metal-catalyzed template synthesis of metal tetrasulphophthalocyanines have recently been reported by Williams and Busch[12], the Co(II) and Ni(II) chelates having been prepared in 80 to 90 per cent yields, respectively. Busch and coworkers have found the template method very efficient for the synthesis of several macrocycles, two of which are illustrated in *Figure 4*. In the presence of Ni(II) and Cu(II) salts *o*-aminobenzaldehyde condenses about the metal ion as a tetradentate ligand, tetrabenzo-b,f,j,n-1,5,9,13-tetraazacyclohexadecine [13, 14], which forms square planar metal chelates. The Ni(II) chelate is diamagnetic.

In the absence of metal ion, mercaptoethylamine (*Figure 4*) reacts with α-diketones to form thiazolidines, which are in equilibrium with small amounts of the corresponding Schiff bases, and are derived from them by the addition of the mercapto group across the imine double bond [15, 16]. The metal ion shifts this equilibrium entirely in favour of the bis Schiff base, because of the greater stability of its metal chelate over that formed by the corresponding thiazolidine[17, 18]. The negative mercaptide groups of this Ni(II) chelate have been condensed with α,α′-dibromo-*o*-xylene, to produce the macrocycle illustrated in *Figure 4*, the S,S′-*o*-xylyl-2,3-butanedione-bis(mercaptoethylamine)-nickel(II) ion[2]. The synthesis of these and other macrocycles through metal template reactions has recently been reviewed by Busch and coworkers[2, 14, 18].

FROM o-AMINOBENZALDEHYDE



(Melson and Busch, 1963)

ALKYLATION OF MERCAPTOETHYLAMINE SCHIFF BASES

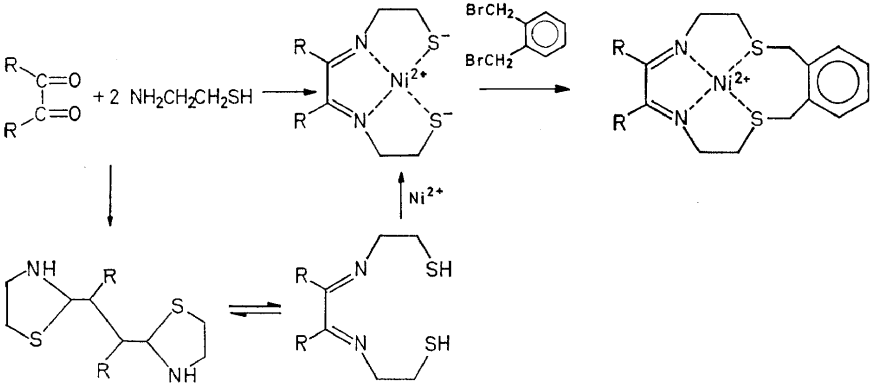
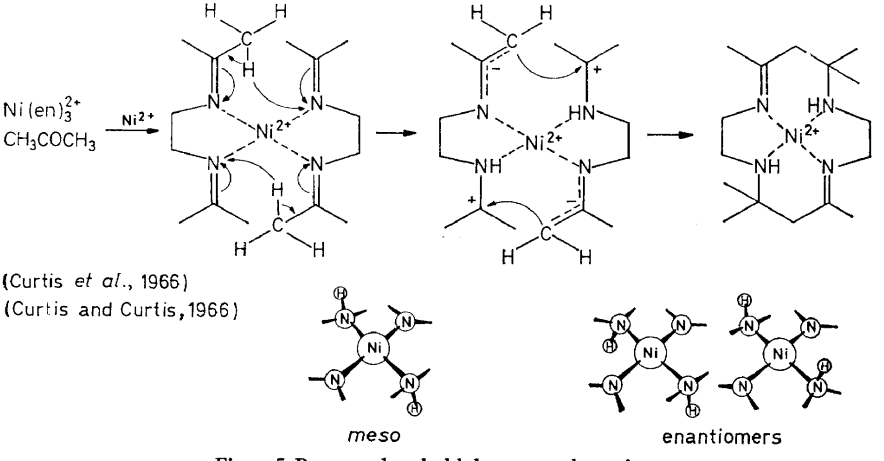


Figure 4. Template synthesis of macrocyclic rings

Another interesting metal template synthesis of a macrocycle is the base-catalyzed condensation of acetone with the trisethylenediamine Ni(II) ion in non-aqueous solvents (*Figure 5*) reported by Curtis *et al.* [19–24]. A similar



(Curtis *et al.*, 1966)
(Curtis and Curtis, 1966)

Figure 5. Base catalysed aldol type condensation

reaction has been carried out with Cu(II) as a catalyst. The cyclization reaction is illustrated as occurring through the condensation of adjacent activated methyl and imine groups of two Schiff bases, derived from acetone and ethylenediamine, while coordinated to the metal ion. This reaction scheme appears entirely feasible, but the details of the mechanism have yet to be demonstrated. The product, the hexamethyltetraazacyclotetradecadiene-Ni(II) cation, is extremely stable, and is not attacked by boiling concentrated acids or bases.

(b) Nucleophilic reactions

1. *Solvolysis.* Solvolysis reactions probably constitute the most numerous class of nucleophilic reactions of metal chelate compounds. Metal ions would be expected to generally promote solvolysis reactions, in which the chelated ligand reacts with an electron donating solvent molecule, since the electronic interaction of a ligand with a metal ion would always increase its reactivity toward nucleophilic reagents. In many cases the influence of the metal ion on such ligand reactions are relatively weak. There are certain examples of this type of reaction, however, in which the catalytic effect of the metal ion is very strong. Such large catalytic effects are observed when the ligand donor groups are in positions that hold the metal close to the reactive centre, or when the formation of a stable metal chelate is the result of the solvolysis reaction.

The hydrolysis of alpha amino acid esters and amides, illustrated in *Figure 6*, is an example of this type of strongly metal-catalyzed solvolysis reaction. Metal ion catalysis of amino acid ester solvolysis has been reported by Kroll[25] and by Bender and Turnquest[26]. It is now known that alpha amino esters coordinate transition metal ions through the amino nitrogen and carbonyl oxygen. The additional polarization of the carbonyl oxygen thus achieved facilitates nucleophilic attack of the carbonyl carbon by a polar water molecule to produce a number of reactive intermediates in rapid equilibrium, differing in the positions of attachment of protons and the metal ion (additional reasonable intermediates are probably also present). The splitting out of a mole of alcohol results in solvolysis, while the splitting out of a mole of the solvent regenerates the original ester, with exchange of the carbonyl oxygen. Generally the catalytic effect of the metal ion parallels the stabilities of the corresponding amino acid chelates, in agreement with the concept that metal chelate formation is the principal driving force of these reactions (i.e. the transition state metal chelate closely resembles the metal amino acid chelate that is finally formed). Alcohol solvolysis (ester exchange) follows a similar mechanism.

Alexander and Busch[27] prepared complexes of amino acid esters coordinated to bisethylenediaminechlorocobalt(II) in a unidentate fashion through the terminal amino group, with aminoester and chloro groups in *cis* positions. This complex was found to hydrolyze very slowly, but a new complex was formed on the addition of Hg(II) ion that hydrolyzed quite rapidly. It was concluded that the chloro group was removed by the Hg(II) ion, resulting in bidentate coordination of the amino ester through the terminal amino group and the carbonyl oxygen, thus giving rise to strong

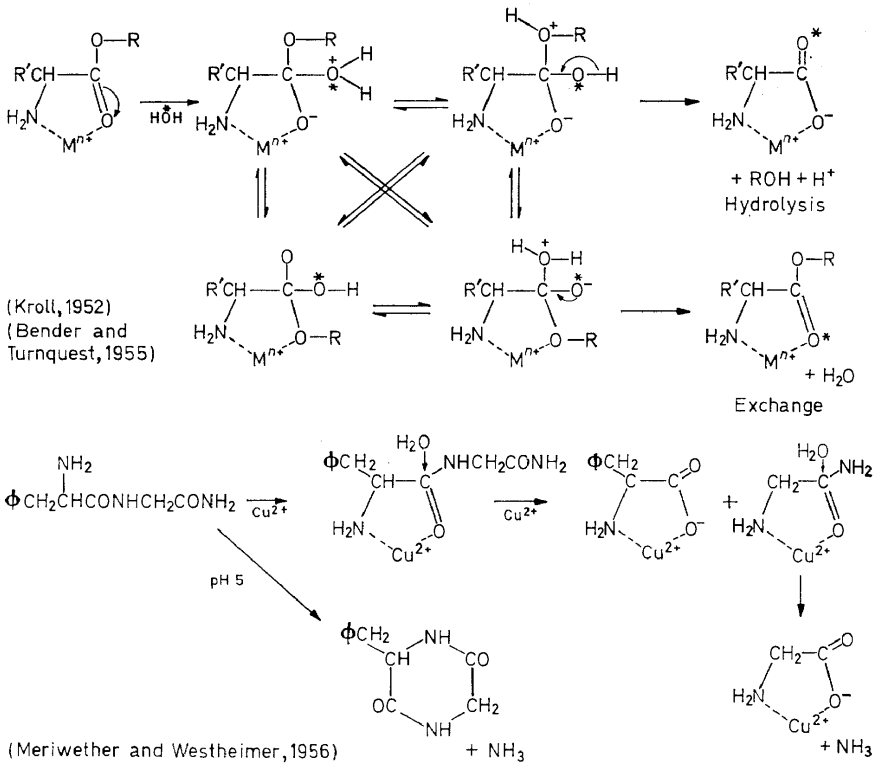
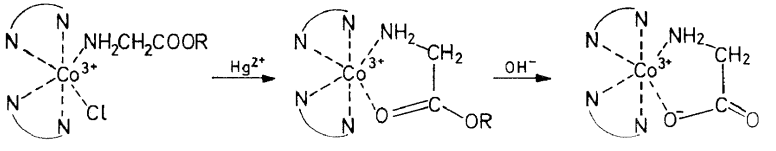


Figure 6. Solvolysis of esters and amides

catalysis of solvolysis by the metal ion. Each of the following complexes were identified in solution by their characteristically different carbonyl frequencies.



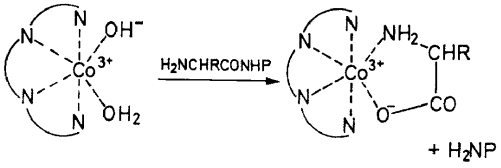
Further examples of ester hydrolysis in which catalysis by metal ion is facilitated by auxiliary chelating groups in the substrate are: esters containing α and β-carboxylate ions[28, 29] and phosphate esters containing a β-coordinating group on the alcohol moiety[30–32]. An extreme example of metal chelate formation as a driving force in ester hydrolysis is the recent report of Cu(II) and Sm(III) catalysis of the hydrolysis of the monoethyl ester of nitrilotriacetic acid by Angelici and Leach[33]. In this case three of the four donor groups in the NTA chelate finally formed are already present in the substrate before hydrolysis.

Thiolesters are a striking example of the relationships between the nature of the chelating donor atoms of the ligand and the catalytic effect of the

metal ion. Mercuric ion has been found to be especially effective in catalyzing the hydrolysis of thiol esters such as acetyl-S-coenzyme A[34] and acetoacetyl-S-coenzyme A[35], reflecting the high affinity of the Hg(II) ion for sulphur donors and the fact that the reaction product is a mercury chelate containing a mercaptide–metal bond. Similar effects should be observed with other metal ions having high affinity for mercaptide and sulphide donors, such as those of Zn(II), Cd(II), Sn(II), and Pb(II).

Meriwether and Westheimer[36] have studied the hydrolysis of amino acid amides in the presence and absence of Cu(II), Ni(II), and Co(II) ions. In the absence of metal ions, a nearly quantitative yield of benzyl diketopiperazine is obtained from phenylalanylglycylamide at pH 5 and 75°. In the presence of the Cu(II) ion, the ratio of hydrolytic cleavage to diketopiperazine formation increased by a factor of 200. The mechanism of hydrolysis to produce both phenylalanine and glycine is indicated in *Figure 6*. The lack of even greater catalytic reaction is probably due to the formation of an appreciable amount of relatively stable peptide chelates that involve displacement of the peptide proton by the metal ion.

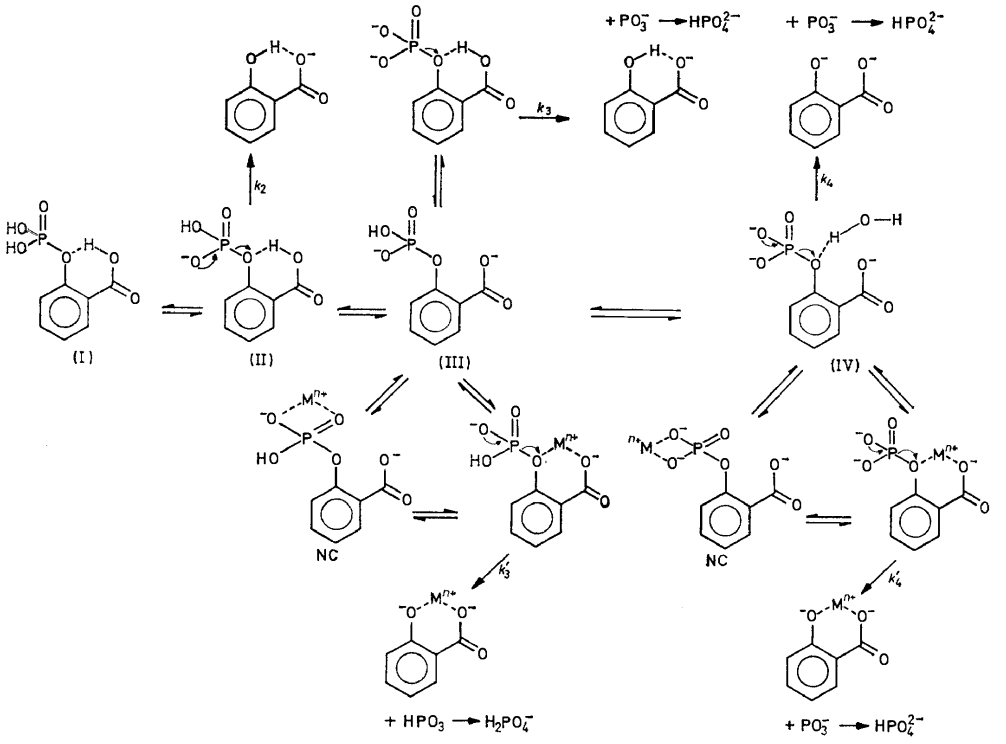
Collman and Buckingham[37] have reported the hydroxoaquotriethylenetetraminecobalt(III) to be an excellent reagent for the hydrolytic cleavage of single N-terminal amino acid residues from peptides, to give the corresponding bidentate amino acid complexes, as shown by the equation:



The reaction proceeds through coordination of the terminal amino group and the adjacent carbonyl oxygen to the cobalt(III) ion to produce a chelated reactive intermediate which is not shown. Nucleophilic attack on the metal ion-activated intermediate by a hydroxide ion generates the amino acid chelate and the remaining peptide moiety.

Salicyl phosphate hydrolysis. Metal ion catalysis of the hydrolysis of salicyl phosphate is an interesting example of metal chelate formation as a driving force in solvolysis[38, 39]. The spontaneous hydrolysis rates, with a maximum at pH 5·2 can be resolved into rates for the mono-, di-, and trinegative forms of the ester, as indicated in *Figure 7*. Divalent metal ions do not catalyze the hydrolysis of the monoanion, a result that is not surprising in view of the low affinity of metal ions for this diprotonated ligand. Positive metal ion catalysis of the dianion was observed. The strongest catalytic effect, however, is with the completely dissociated ligand, which hydrolyzes 100 times faster than the corresponding mono protonated chelate. This is in marked contrast to the relative rates for the spontaneous (i.e. metal-free) systems, for which the fully dissociated species hydrolyzes 2000 times more slowly than the monoprotonated species.

The mechanisms indicated for the metal-free hydrolysis of all three ionic species are analogous to those suggested by Bender and Lawlor[40] for the binegative form. The mononegative species (II) should hydrolyze more



Spontaneous Hydrolysis, sec^{-1}

$K^{II} = 1{\cdot}3 \times 10^{-5}$

$K^{III} = 7{\cdot}6 \times 10^{-5}$

$K^{IV} = \sim 4 \times 10^{-8}$

Metal Catalysis, $sec^{-1}\,M^{-1}$

$K^{II}_{Cu} = \sim 0$

$K^{III}_{Cu} = 4{\cdot}0 \times 10^{-2}\, K^{III}_{VO} = 3{\cdot}3 \times 10^{-1}$

$K^{IV}_{Cu} = \sim 3{\cdot}7$

Mont and Martell (to be published)

Murakami and Martell (1963)

Figure 7. Metal ion catalysed hydrolysis of salicyl phosphate

slowly than (III) since the proton bound to one of the phosphate oxygens would polarize the P—O ester bond in the direction opposite to that required by phosphorus–oxygen fission. The effect of the phosphate bound proton, however, is not as great as it might be, since its influence is partially counteracted by the greater availability of the carboxylate proton for transfer to the salicylate phenolate oxygen. For the trinegative species (IV) there are no protons available for intramolecular transfer to the phosphorus ester oxygen, and the slower transfer from the solvent offers the only possibility for promoting the solvolysis reaction.

Catalytic metal ions may combine with the substrate in at least two ways. Coordination with the phosphate oxygens, as shown, can only result in slowing down the reaction. Thus the rate of hydrolysis of the phosphate-coordinated chelate MHL^{n-2} (where H_3L is salicyl phosphate) should hydrolyze at a slower rate than HL^{2-} (formula III). Another probable

metal-coordinated species is one in which the metal ion is coordinated to the carboxylate group and the phosphate ester oxygen. This structure is analogous to the reactive protonated form of (II) and resembles most closely the structure of the final product, the metal salicylate chelate. A similar mechanism has been suggested by Murakami[41] for the metal–ion catalysed hydrolysis of of 2-pyridyl methyl phosphate.

Metal catalysis is found to be most effective for the most basic form of the substrate, where no internal protons are available for catalysis. Here also, the reactive form indicated in *Figure 7* is that which resembles the product most closely.

The examples of metal chelate catalysis illustrated in *Figure 7* illustrate the analogy between the catalytic activities of metal ions and protons. The electronic shifts in the ligand are quite similar for both metal ion and proton catalysis. One of the characteristic advantages of a metal ion as a catalyst is its availability at high pH, under which conditions protons are not available from the solvent, or from the ligand. Although metal ions have been called "super-protons" because of this characteristic, it should be borne in mind that the electronic interaction of a divalent metal ion with a ligand is considerably less than that of a proton, as is readily verified from shifts in electronic spectra. The superior qualities of a metal ion catalyst, therefore, is restricted to its availability at high pH.

2. *Transphosphorylation.* Non-enzymatic transphosphorylation reactions, studied with ATP and phosphate as an enzyme model system, is an example of a metal ion-catalyzed nucleophilic reaction illustrated in *Figure 8.* The suggested mechanism involves nucleophilic attack on the terminal phosphate

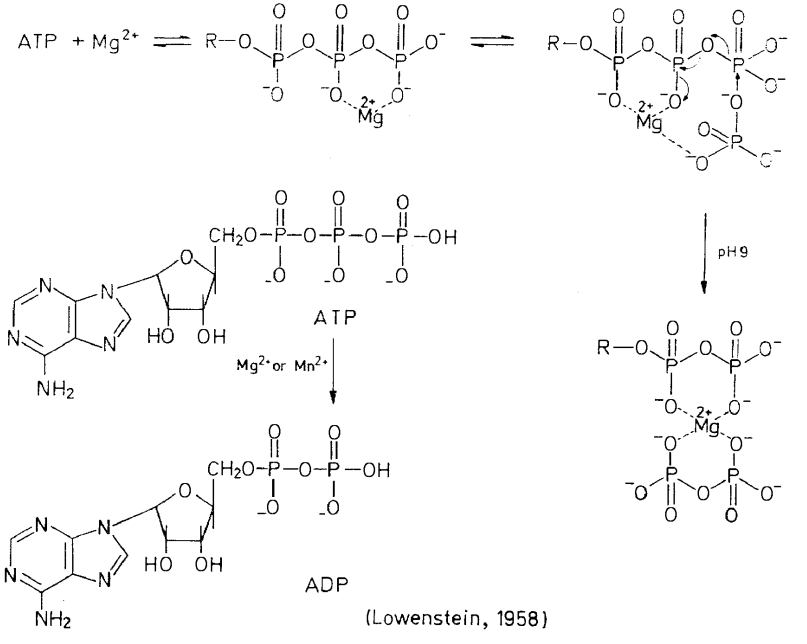


Figure 8. Non-enzymic transphosphorylation

atom of ATP by the phosphate anion. The metal ion may also coordinate with the phosphate anion, holding it in a position favourable for nucleophilic attack. It seems that one of the important driving forces of the reaction is the formation of two metal chelate rings with the reaction products, one with each pyrophosphate group. Considerably less coordination can occur between a metal ion and the reactants, and only one chelate ring can be formed. Ca(II), Cd(II) and Mn(II) ions were found to be effective as catalysts[42]. The same extent of metal ion catalysis is not possible with the corresponding acylation reaction. In this connection, however, it is interesting to note that quite different metal ions are found to be effective as catalysts. Thus the Be(II) ion seems to be the most effective for conversion of ATP and acetate ion to ADP and acetyl phosphate[43].

3. Schiff Base Formation. Metal ion catalysis of Schiff base formation is another example of a nucleophilic reaction (of the amine nitrogen on the carbonyl group). The driving force behind these reactions is the relatively high stability of the Schiff base chelate that is formed. This is demonstrated by several factors. For example when a Schiff base does not form a chelate compound which is significantly more stable than that formed from the parent amine (e.g., a polyamine), then the metal ion does not catalyze Schiff base formation. In fact, metal ions are good catalysts for hydrolysis of the Schiff base to the polyamine chelate and the corresponding carbonyl compound, as pointed out by Eichhorn[44, 45] and others[46]. On the other hand, the equilibrium favouring the formation of Schiff bases of mercaptoethyl amine and α-diketones is shifted very strongly in the direction of the Schiff base by formation of the corresponding metal chelate[16], as is indicated in *Figure 4*. A similar effect of metal ions on the formation of bisacetylacetoneethylenediamine (as its metal chelates) has also been pointed out[1].

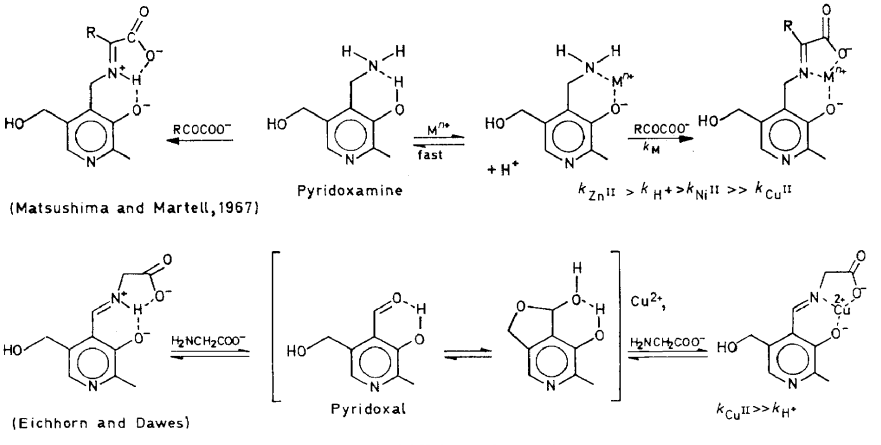


Figure 9. Schiff base formation

The mechanism of Schiff base formation involves nucleophilic attack by the amino nitrogen atom on the carbonyl group of the aldehyde or ketone followed by the elimination of water. Since, however, most metal ions have higher affinities for the polyamines than for the carbonyl compounds

the latter are not activated while the amines are deactivated by metal ion coordination. Therefore the principal driving force in Schiff base formation is clearly the stability of the chelated product. These factors are illustrated by the two examples of Schiff base formation given in *Figure 9*. The Cu(II) ion, which forms the most stable chelate of pyridoxamine and α-keto-isovaleric acid[47, 48], is the poorest catalyst kinetically. If sufficient time were allowed however, the Cu(II) ion would produce the highest yield of Schiff base (if there were no subsequent reactions, as indicated below). Similarly, Cu(II) ion was found to be the most effective of several metal ions in forming the metal chelate of the pyridoxal-glycine Schiff base, because of the favourable equilibrium involved[49].

Thus it is seen that the equilibrium effect of metal chelate formation is an important driving force even when the kinetic effect of the metal ion is one of deactivation.

4. Stereospecific Polymerization. Because of the steric requirements of the coordination sphere of the metal ion, metal chelate catalyzed polymerization frequently proceeds in a stereospecific manner. The two examples illustrated in *Figure 10* involve nucleophilic attack of one coordinated ligand on another. In the first example, polymerization of butadiene on a Rh(III) catalyst in homogeneous solution results in stereospecific formation of a *trans* polymer[50, 51]. Initial combination of Rh(III) with butadiene and water results in the addition of a hydroxide ion to the ligand and formation of a negative π-allyl group which coordinates to the metal ion. This negative group then attacks an adjacent coordinated butadiene molecule, and a new π-allyl group is generated. It is seen from the third and fourth formulae that simultaneous coordination of the π-allyl and the isolated double bond of the first-coordinated butadiene residue is quite possible, and it therefore seems that one of the driving forces of the reaction is the formation of a

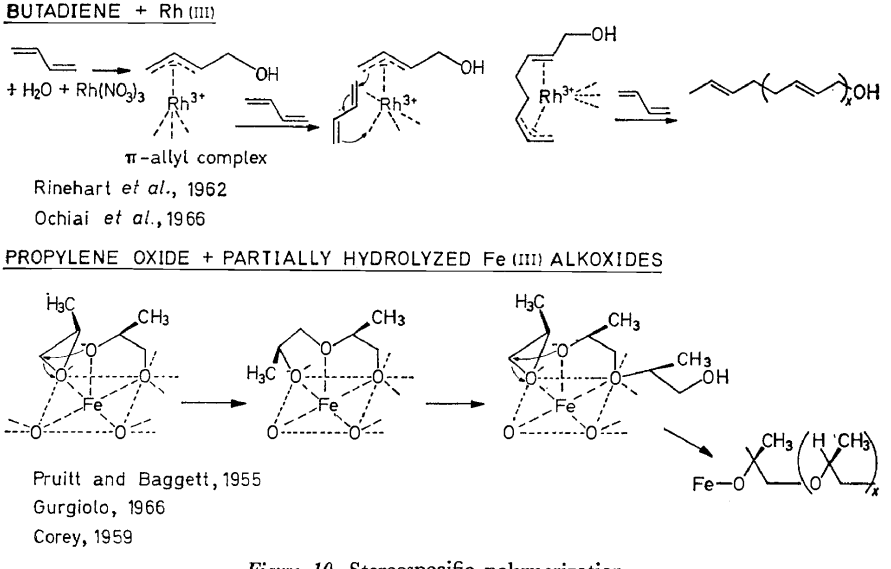


Figure 10. Stereospecific polymerization

π-bonded type of metal chelate compound. The steric requirements of chelate formation are seen as the reason for stereospecific *trans* polymerization since the formation of a bond between the π-allyl bound ligand and an additional butadiene monomer, with simultaneous coordination of the two π-donor positions, would not be possible without a *trans* configuration of the adduct.

An equally interesting example of stereospecific polymerization through metal chelate formation is the synthesis of isotactic polypropylene oxide on a polynuclear hydroxo-alkoxo iron(III) chelate described by Pruitt and Baggett[52] and more recently by Gurgiolo[53]. The mechanism given in *Figure 10* follows the general steric requirements for formation of the organic polymer described by Corey[54], but suggests new detail for the mechanism of polymerization at the coordination site, and in this respect represents a modification of the suggestions of Gurgiolo[53]. Remembering that the negative oxygen at the end of the coordinated alkoxide or partially coordinated polymer undergoes nucleophilic attack on the propylene oxide carbon which is farthest from the electron-donating methyl group, then the propylene oxide and the negative ligand must line up on the polynuclear metal chelate catalyst as indicated in *Figure 10*, with the methyl groups on opposite sides of the two adjacent organic ligands. When the new propylene oxide moiety has combined and shifts around it is seen that the two methyl groups are on the same side of the growing polymer chain and stereospecificity has been achieved. The catalyst employed in this reaction is highly polynuclear and heterogeneous with an empirical formula of $Fe_2C_3H_{10}O_6$. It was suggested[53] that a terminal coordinated alkoxide group on the surface of the catalyst is available for nucleophilic attack on a reactive coordinated monomer unit as indicated in *Figure 10*. Other types of catalysts have been employed to achieve varying degrees of specificity. A homogeneous Fe(III) alkoxide catalyst, soluble in ether, has been employed by Gee *et al.* [55, 56]. Also, Vandenberg[57] has described a catalyst consisting of monoacetylacetonoaluminum(III) alkyl, hydrolyzed with water, which is effective in the stereoregular polymerization of olefin oxides. It should be pointed out that all of the catalysts described above also give atactic polymers of olefin oxides when reaction conditions and/or methods of preparation of the catalyst are modified.

(c) Electrophilic substitution

Metal ions can promote electrophilic substitution reactions involving a coordinated ligand by first displacing a positive atom or group, usually a proton. The resulting negative ligand may then react with an electron-accepting reagent. Examples of electrophilic substitution reactions in which a major driving force is the formation of metal chelate rings are given in *Figure 11*.

The metal chelates of malonic acid monoesters may be acylated through the initial loss of a proton from the ligand. Ireland and Marshall[58] have reported the acylation of the Mg(II) chelates of malonic acid monoesters, as indicated in *Figure 11*. The acyl carbon atom reacts with the carbanion at the alpha carbon atom to produce a keto acid ester, which then decarboxylates to give the more stable chelate of the corresponding β-keto ester.

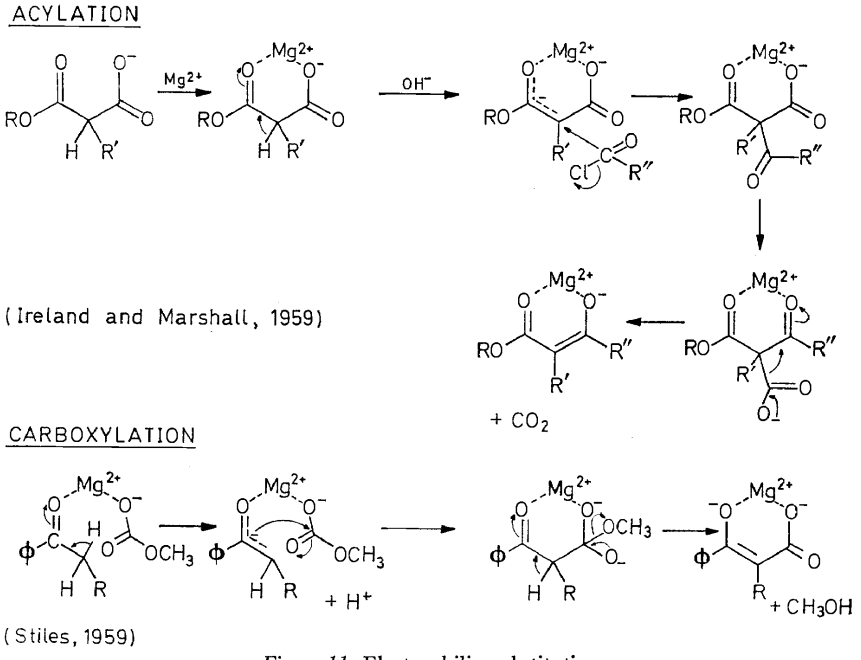


Figure 11. Electrophilic substitution

Stiles *et al.*[59, 60] have reported the carboxylation of ketones containing an active alpha hydrogen atom with magnesium methyl carbonate (CO_2 + magnesium methylate). The driving force of the reaction seems to be the formation of the magnesium chelate of the corresponding β-keto acid. The suggested mechanism involves initial enolization of the ketone with simultaneous displacement of the alpha proton. Simultaneous coordination of the resulting enolate and methyl carbonate by the metal ion (*Figure 11*) is seen to facilitate electrophilic attack of the carbonate carbon on the alpha position of the enolate ion. Loss of a mole of methyl alcohol then produces the magnesium chelate of the β-keto acid.

Similar reactions with magnesium and aluminium methyl carbonates were effective in converting nitroparaffins to nitroacetic acid and alkyl derivatives of nitroacetic acid[59, 60].

(d) Molecular rearrangements

Rearrangement of groups in a chelating ligand is frequently the result of metal ion coordination. Examples of metal chelate catalyzed molecular rearrangements in which metal chelate ring formation is a significant driving force are given in *Figures 12* and *13*.

After it was pointed out[61] that metal chelate ring formation may stabilize cyclobutadiene and its derivatives, there have been four successful attempts to prepare these unusual π-complexes[62–65]. The first preparation of a cyclobutadiene derivative, tetramethylcyclobutadiene, involved the dechlorination of tetramethyldichlorocyclobutiene to tetramethylcyclobutadiene[62] in the presence of nickel(II). The product, tetramethylcyclo-

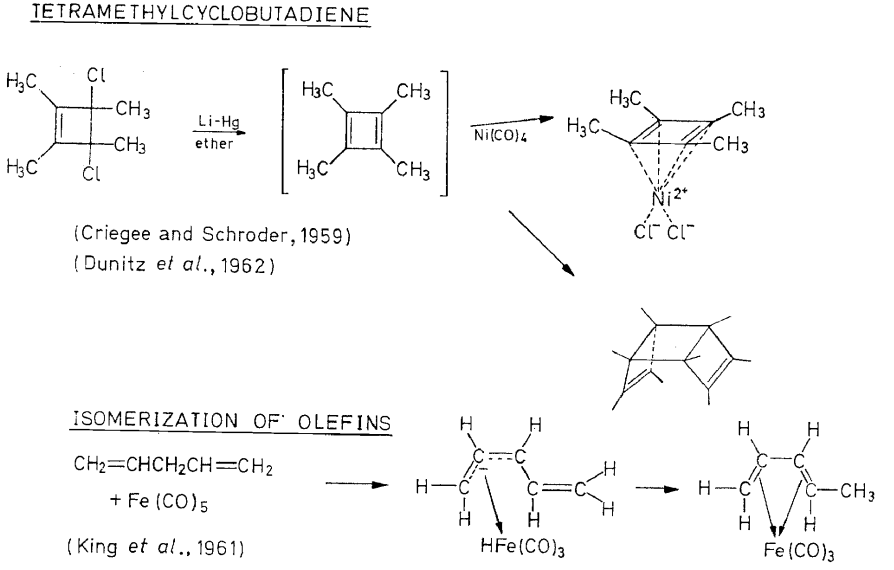


Figure 12. Template synthesis of π-complexes

butadiene nickel(II) chloride is stabilized with π-bonded chelate rings (*Figure 12*) formed by the coordination of two pairs of π-electrons to the nickel(II) ion. In the absence of a strongly π-bonded metal ion, the cyclobutadiene is probably formed as an unstable intermediate, but rapidly polymerizes as indicated in *Figure 12* to give a dimer of cyclobutadiene. Similar π-bond stabilization of cyclobutadiene and its derivatives by transition metal coordination has been reported for the formation of the tetraphenylcyclobutadiene iron tricarbonyl complex[63], of the tetraphenylcyclobutadiene nickel(II) bromide complex[64], and of the unsubstituted cyclobutadiene silver(I) nitrate complex itself[65].

Metal catalyzed isomerization of olefins frequently occurs so as to produce π-bonded metal chelate rings when such structures are possible by double bond migration of non-conjugated dienes and similar substances. For example 1,4-pentadiene readily isomerizes to 1,3-pentadiene in the presence of iron carbonyl, as is indicated in *Figure 12*[66]. The mechanism is pictured as involving the formation of a π-allylhydridoiron intermediate. The ligand then accepts a proton from the iron to generate the conjugated ligand in the form of the π-bonded Fe(0) chelate.

An interesting metal chelate-catalyzed benzilic acid rearrangement has recently been described by Black[67]. In the absence of strongly coordinating metal ions (i.e., in the presence of alkali metal ions) benzilic acid type rearrangement of 2,2′-pyridyl requires strong alkali and high temperatures, and the product readily decarboxylates on acidification. In the presence of Ni(II) or Co(II), however, rearrangement occurs under mild conditions in nearly quantitative yield to give the corresponding octahedral (2:1) terdentate chelates, which are quite stable in acid solution. The mechanism of the reaction (*Figure 13*) is picured as involving preliminary coordination of the metal ion in a bidentate fashion, promoting nucleophilic attack by the

hydroxide ion on the carbonyl carbon. The resulting carbonyl addition product has a tetrahedral carbon atom which can coordinate the metal in a terdentate fashion. The stability of the chelate formed can be greatly increased by bond migration to give a six-membered ring involving the two pyridyl nitrogens, and a second six-membered ring system involving the carboxylate oxygens. The resulting octahedral chelates of Co(II) and

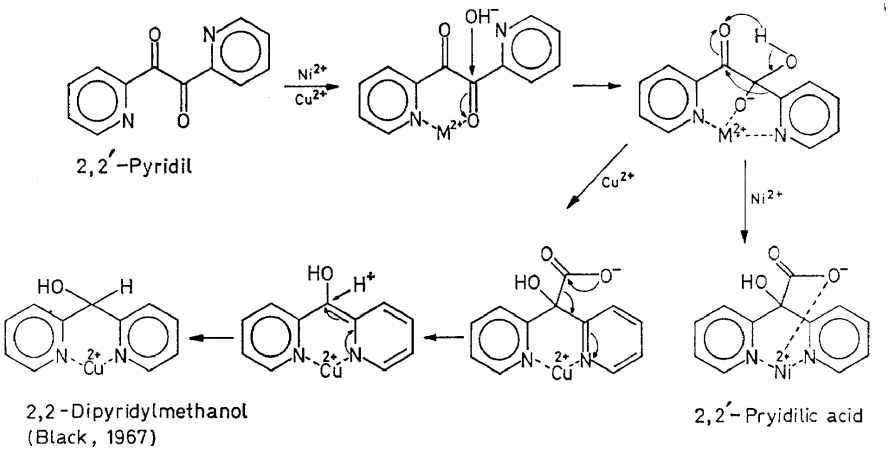


Figure 13. Benzilic acid rearrangement

Ni(II) are stable toward decarboxylation. However, when Cu(II) is the catalyst, the carboxylate group is not stabilized by coordination, and decarboxylation takes place readily to give the square planar chelate of bidentate 2,2′-dipyridylmethanol. Thus the steric requirements of the metal ion are seen to greatly influence the nature of the product obtained.

(e) Chelate ligand displacement reactions

It has recently been pointed out by Margerum and coworkers[68] that the rate of displacement of one chelated ligand from a metal ion very strongly depends on the number of chelate rings that can be formed with the incoming ligand. An example of this type of reaction is illustrated in *Figure 14*, which indicates the suggested mechanism[68] for the displacement of EDTA by triethylenetetramine (trien) from Ni(II) and Cu(II) ions. The trien free base is more reactive than any of its protonated forms, but rapid rates of reaction are also observed for the mono- and diprotonated species. When the degree of protonation is greater than 2 protons per ligand, the displacement reaction becomes extremely slow. These facts are explained by the proposed mechanism in *Figure 14*, which involves the formation of a mixed ligand chelate as the intermediate in which the incoming ligand occupies three positions in the coordination sphere, and one of the nitrogens of EDTA has been displaced. The intermediate has two positions for protonation that will only slightly decrease its stability (i.e., on each of the uncoordinated nitrogen atoms). When three protons are present, however, this intermediate cannot form, or forms to only a very slight extent, thus explaining the observed sharp drop in reaction rate.

Further support for the proposed mechanism is provided by the influence

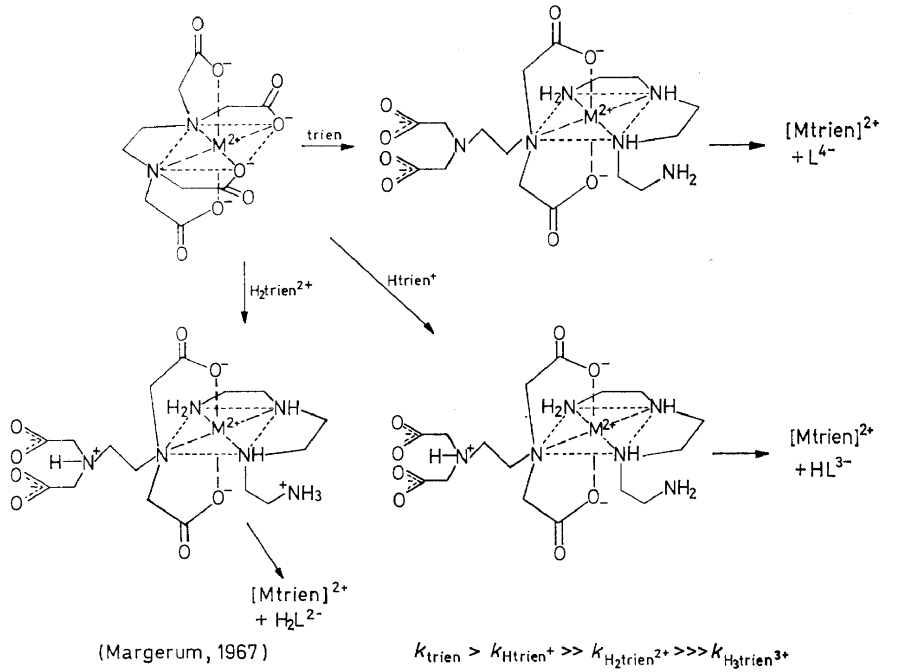


Figure 14. Ligand displacement reactions

on rate of the structures of the incoming and outgoing ligands. Ethylenediamine does not displace EDTA, since it cannot form the terdentate intermediate, but does form stable mixed ligand chelates. Diethylenetriamine (dien) forms an unstable mixed ligand chelate which is rapidly converted to the dien-metal chelate. In this case only one proton can be added to the intermediate without drastically lowering the reaction rate, in accord with the proposed mechanism. With tetrakisaminoethylethylenediamine (penten) three protons are accommodated with only a slight lowering of the rate.

The proposed mechanism is also supported by the fact that the cyclohexanediaminetetraacetate (CDTA) anion is displaced at a very slow rate, in accord with the fact that it is sterically impossible to form the mixed ligand intermediate in this case. Similarly, dien does not form an intermediate with CDTA, but displaces it in a single very slow step.

(f) Decarboxylation

The carboxylation of β-keto acids containing an α-keto acid function is a classical example of a metal chelate catalyzed reaction. Its inclusion within this class of reactions in which the driving force for metal chelate catalysis involves metal chelate ring formation is due to the fact that the intermediate formed as the result of decarboxylation closely resembles the oxalate chelate of the metal ion[69], as indicated in *Figure 15* for oxaloacetate. In accordance with the mechanism shown, the rate constants for metal ion

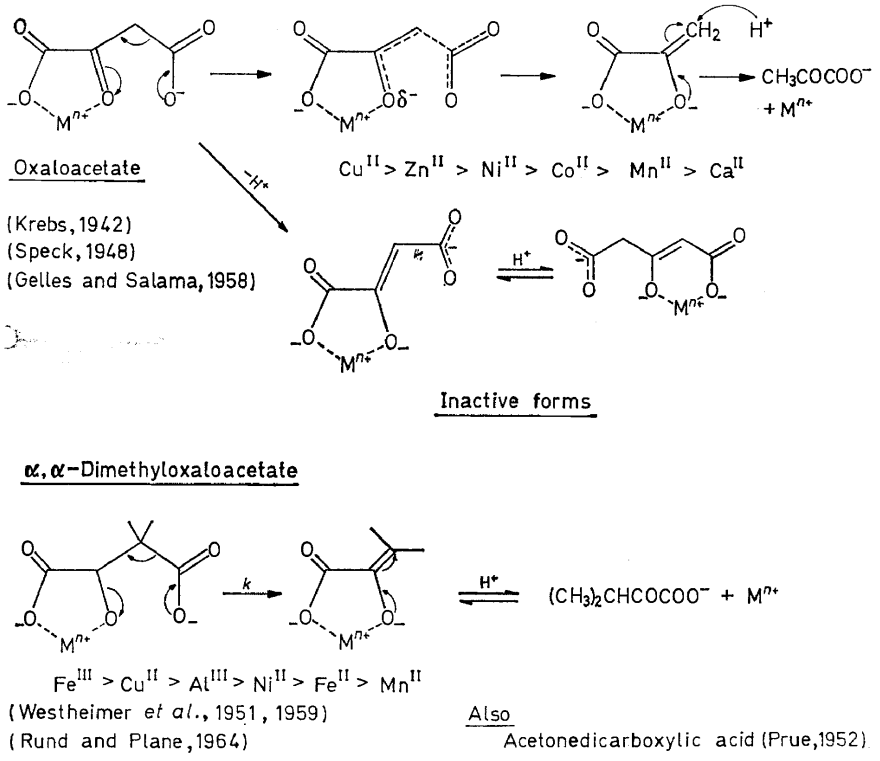


Figure 15. Decarboxylation

catalysis were shown[69] to have a linear relationship to the stability constants of the corresponding metal oxalates, whereas there was no linear correlation with the stabilities of the metal oxaloacetates.

The reaction mechanism involves an electron pair shift toward the metal ion, which results in the breaking of a C—C or a C—H bond. If a C—C bond is broken, decarboxylation takes place, as indicated. If a C—H bond is broken, the dissociation of a proton from the carbon atom adjacent to the ring (i.e., enolization of the carbonyl group) leads to the formation of stable chelates in which the ligand has an additional negative charge and hence does not undergo decarboxylation. These metal catalyzed reactions have been studied in detail by a number of investigators[70–73].

The transition metal ion-catalyzed carboxylation of an analogous ligand, acetonedicarboxylic acid[74] is believed to take place by a similar mechanism. In this case both carboxylic acid groups have a β-keto function, so that the metal ion is held by a β-keto acid group which in the transition state resembles a malonate chelate. The reaction rates were accordingly found to correlate closely with the thermodynamic stabilities of the malonate chelates of the metal ions.

The kinetics of metal ion-catalyzed hydrolysis of dimethyloxaloacetate, indicated in *Figure 15*, has been described by Steinberg and Westheimer[75].

The inactive metal chelates formed with oxaloacetate cannot form in this case. A strongly absorbing intermediate that was detected in this system is the deprotonated metal chelate indicated in *Figure 15* as the product of the decarboxylation reaction. This enolate is then converted to the final product by the addition of a proton. The relative catalytic effects of the metal ions investigated are similar to those reported for oxaloacetate decarboxylation.

An interesting metal chelate-catalyzed stereoselective decarboxylation reaction, recently reported by Asperger and Liu[76], is illustrated in *Figure 16*. The L-*cis*-β form of the α,α'-dimethyltriethylenetetraminecobalt(III) ion combines with D,L-α-methyl-α-aminomalonate to give the mixed ligand diastereoisometric chelate indicated by the first formula. Decarboxylation occurs by the same mechanism as that illustrated in *Figure 15* to give a final mixed ligand chelate of alanine in which the L-alanine enantiomer is enriched by about 25–30 per cent. Thus the steric influence of the optically active ligand coordinated to the metal ion favours one of the diastereoisomeric pairs over the other in the reactions illustrated. It is not known whether the stereoselectivity is achieved in the formation of the malonate chelate, in the decarboxylation step, or in both.

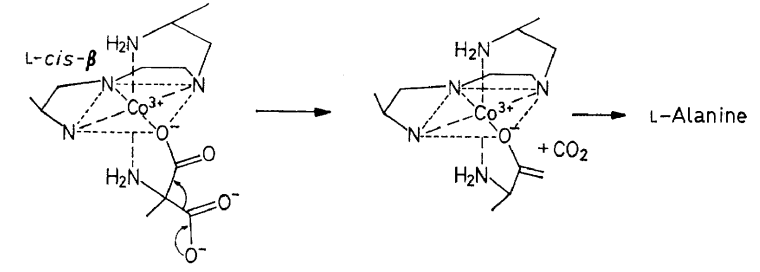


Figure 16. Asymmetric synthesis of L-alanine

This reaction is merely a single example of a general reaction type that has wide applicability. It should be possible to achieve similar or even better stereoselectivity in any metal chelate catalyzed reaction in which an optically active chelate reacts with a racemic substrate.

II. SUBSTITUTION AND ISOMERIZATION REACTIONS (METAL CHELATE RINGS ALTERED)

(a) Nucleophilic substitution

Since coordination to a metal ion results in an electron shift away from the ligand, the latter will always be activated toward nucleophilic reagents. The extent of the activation will depend on the extent of electronic interaction with the metal ion. Thus all of the nucleophilic reactions described above would be metal ion promoted even if the products were not metal

chelates, or if no change in chelate ring structure took place as a result of the reaction.

Recent examples of this type of reaction may be found in peptide synthesis reactions, ester exchange, and amide formation of chelated amino esters illustrated in *Figure 17* and reported by Buckingham and Sargeson[77]. The coordination of alpha amino acid esters (as in the case of the ocrresponding amides and peptides from which a proton is not displaced by the metal ion) generally takes place in a bidentate fashion through the terminal amino group and the next adjacent carbonyl oxygen as indicated in *Figure 17*. Activation of the carbonyl group through chelate formation thus facilitates attack by the nucleophilic reagents indicated. The reactions take place very rapidly in non-aqueous solvents.

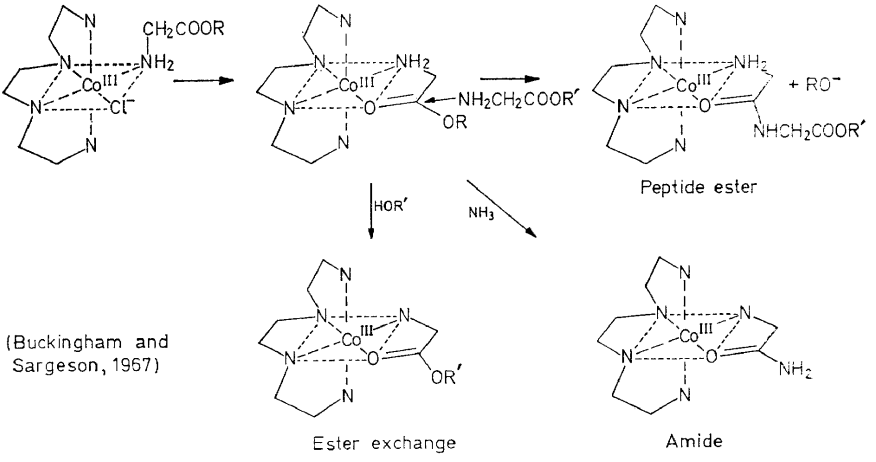


Figure 17. Peptide synthesis

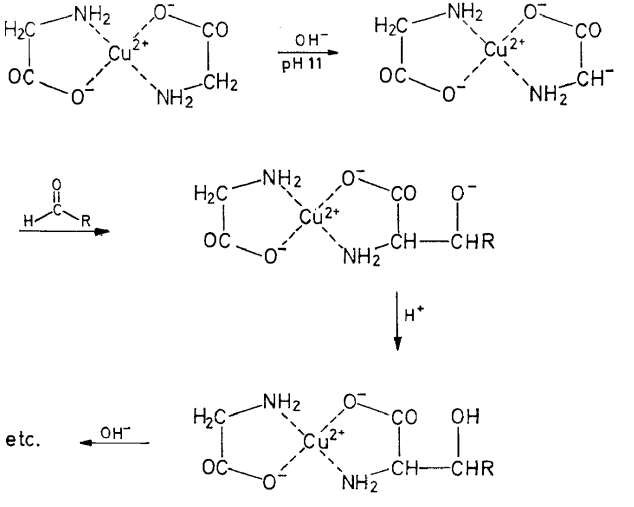
In aqueous solution a competing hydrolysis reaction would also take place, as has been demonstrated by Alexander and Busch[27]. The reactions indicated in *Figure 17* are the first examples of the synthesis of a peptide through the catalytic effect of a metal chelate. Further work in this direction should result in the development of many stereospecific reactions that will be valuable for organic synthesis as well as models of enzyme action.

(b) Electrophilic substitution

In electrophilic substitution reactions of organic chelating ligands, metal ions exert catalytic effects by promoting initial dissociation of a proton from the coordinated ligand. Many reactions of this type are now known, but only a few representative examples can be given here.

Aldol condensation of alpha amino acids and their anions occurs very

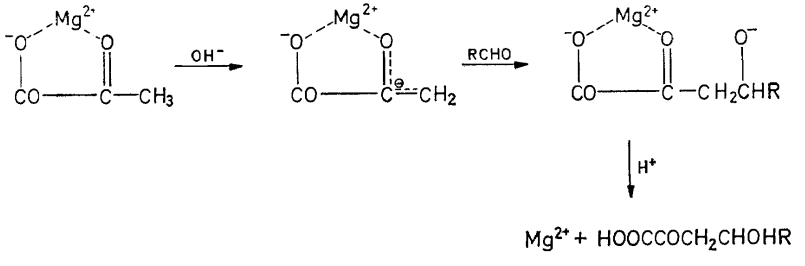
slowly or not at all in the absence of metal ions. On the other hand bis-glycinato copper(II) undergoes aldol condensation between the alpha carbon of the amino acid and aliphatic aldehydes:



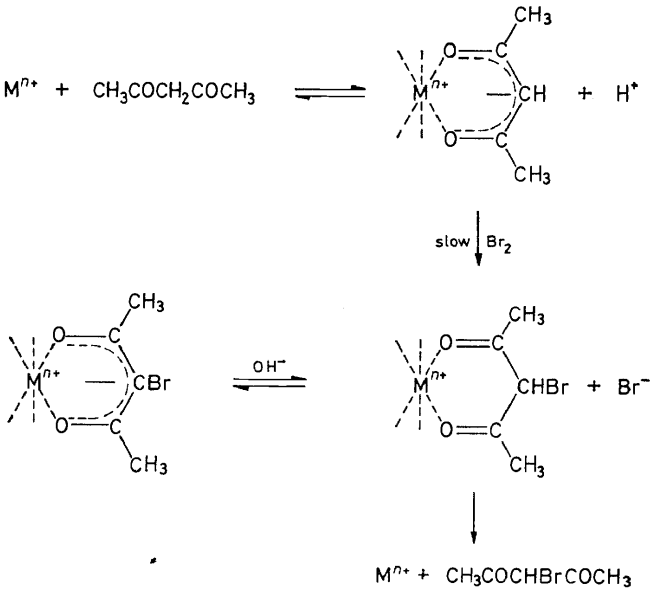
Thus condensation with formaldehyde and with acetaldehyde produces Cu(II) chelates of serine and threonine, respectively[78, 79]. Similar reactions with optically active metal chelates, such as those of Co(III) should result in the asymmetric synthesis of optically active amino acids.

Similar metal ion-catalyzed electrophilic substitution reactions have been carried out with the glycinobisethylenediaminecobalt(III) complex[80]. In this case a stronger catalytic effect was observed because of the greater electrostatic and coordinative interaction of the cobalt(III) ion with the amino acid.

Similar metal chelate-catalyzed electrophilic substitution reactions may be observed in any ligand that can produce an enolate anion by proton displacement, and that has two (or more) donor groups capable of forming a chelate ring with a metal ion. Thus a metal pyruvate chelate condenses with aliphatic aldehydes[81].



Bromination. Another example of an interesting electrophilic substitution reaction is the bromination of a series of metal β-diketone chelates reported by Pederson[82]:



In the presence of relatively small (catalytic) concentrations of the metal ion, the reaction rates are proportional to the stabilities of the metal acetylacetonates (i.e., to the equilibrium concentrations of the metal chelates). Since bromine is in considerable excess with respect to the metal chelate concentration, it is not known whether it is involved in the rate determining step, as indicated. The relative rates observed decrease in the order Cu(II) > Ni(II) > La(III) > Zn(II) > Pb(II) > Mn(II) > Cd(II) > Ca(II) > Ba(II) > H^+. Similar catalytic effects have been observed[82] for the bromination of ethylacetoacetate and 2-carbethoxycyclopentanone.

Many other electrophilic substitution reactions of β-diketone chelates have been reported[83–89]. These include acylation, formylation, and nitration, as well as bromination.

(c) Elimination and isomerization reactions

The displacement of a proton by a metal ion from a chelating ligand produces anions that frequently undergo rearrangements or elimination reactions. If the negative charge is relieved by recombination with a proton the initial ligand may be regenerated, or an isomeric (tautomeric) species can be formed, depending on the position occupied by the proton. Alternatively, the negative charge may be relieved by elimination of an electronegative group from the ligand. Examples of both of these types of metal chelate catalyzed reactions are given below.

Isomerization (tautomerization). Perhaps the best-known example of metal

chelate catalyzed proton isomerization is the metal ion catalyzed transamination of Schiff bases formed from pyridoxal or pyridoxal phosphate and amino acids, and of Schiff bases formed from pyridoxamine or pyridoxaminephosphate and α-ketoacids, first reported by Snell, Metzler and coworkers[90–96], and by Eichhorn and coworkers[49, 97]. Metal catalysis of transamination of Schiff bases derived from pyridoxal and α-amino acids was found to take place with Cu^{2+}, Fe^{3+} and Al^{3+} ions[95]. Recently the rate constants for transamination of the Zn^{2+}, Cu^{2+}, and Ni^{2+} chelates of the Schiff base of pyridoxamine and α-ketoisovaleric acid have been measured (*Figure 18*)[47, 48] and the relative catalytic activities were found to vary in the order $Cu^{2+} > Ni^{2+} > Zn^{2+}$. All of these metal-catalyzed isomerizations of the ketimine chelate to the aldimine chelate were found to take place as a purely first order reaction to about 99 per cent conversion, indicating the relatively much higher stability of the metal chelate of the aldimine over that of the ketimine.

The mechanism of the reaction illustrated in *Figure 18* involves base catalyzed displacement of a proton alpha to the pyridine ring, to produce a ligand species with a negative charge resonating between the alpha positions of the keto acid moiety and the alpha position adjacent to the pyridine ring. Addition of a proton to the keto acid residue produces the aldimine chelate.

These metal–Schiff base chelates also undergo other types of reactions, that are initiated by (i) the displacement of a positive group other than a proton, or (ii) by the reaction of the carbanion intermediate in some manner other than combination with a proton. These reactions will be described in the next section, and under the classification of metal catalyzed rupture of chelate rings (*Figure 24*).

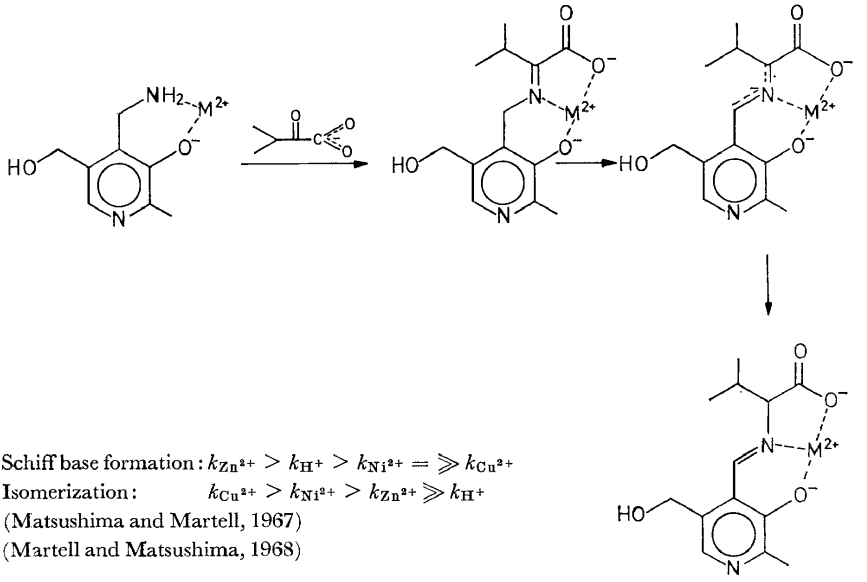
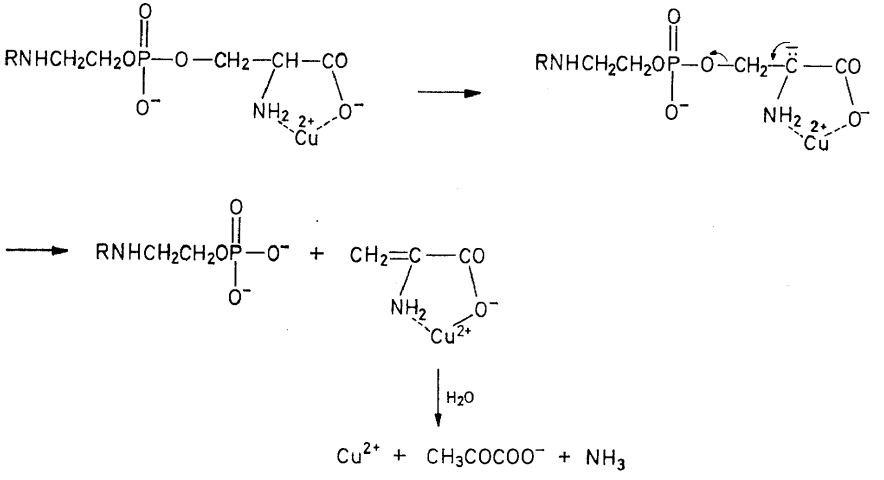


Figure 18. Metal catalysed transamination of pyridoxamine and α-ketoisovaleric acid

Elimination Reactions. The negative carbanion intermediate illustrated in *Figure 18* may also be stabilized by the loss of an electronegative group, as is indicated in *Figure 24.* Thus an electronegative group X (e.g., the hydroxyl group of serine) may be eliminated as a negative ion by an appropriate electron shift. Hydrolysis of the resulting Schiff base produces pyridoxal, the alpha keto acid, and the metal ion.

A similar metal chelate-catalyzed elimination of an electronegative group is the cleavage of a monoesterphosphate group from the Cu(II) chelate of a serine phosphate ester[98], illustrated below.



III. REACTIONS IN WHICH METAL CHELATE RINGS ARE BROKEN

The electronic interaction between a chelating ligand and a metal ion always results in a shift of electrons toward the metal ion. When this occurs the electron density in the chemical linkages can be lowered to the extent that one or more chemical bonds in the ligand are significantly weakened, and rupture of the metal chelate ring takes place. In cases where chemical bonds within the ligand are not broken, the reduction of electron density in the ligand may be sufficient to lower the basicity of the ligand donor groups to the point where the coordinate bonds of the metal chelate are broken. Most metal-ligand interactions resulting in rupture of metal chelate rings involve a redox process in which electrons are transferred from the ligand to the metal ion. There are, however, other types of reactions that are initiated by an electron shift toward the metal ion, but result in internal redox reactions of the ligand with bond rupture, but with no change in valence of the metal ion. Examples of all of these reaction types are given below in parts a, b, and c of this section.

(a) Direct oxidation of the ligand by the metal ion

A classical example of the rupture of metal chelate rings through direct oxidation of the ligand by the metal ion is the decomposition of manganese

(III)–oxalate complexes[99–101] illustrated in *Figure 19*. The mechanism suggested involves a single electron transfer to the metal ion forming a free radical ligand intermediate which is a poorer donor than the original ligand, and hence dissociates readily. Combination with a second Mn(III) ion

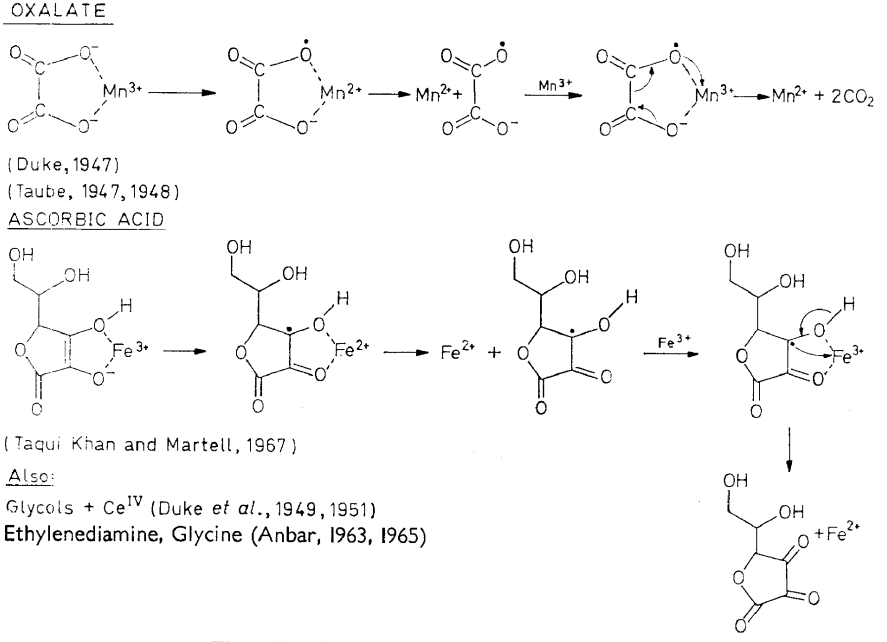


Figure 19. Direct oxidation of ligand by metal ion

completes the electron transfer process and results in rupture of the carbon–carbon bond, completing the conversion of the ligand to carbon dioxide. Similar mechanisms have been proposed for the oxidation of glycols[102, 103] and glycerol[104] by Ce(IV) and for the oxidation of ethylenediamine[105] and glycine[106, 107] by Tl(II) ions.

Although there is no rupture of a carbon–carbon bond, the oxidation of ascorbid acid by Fe(III) ions, recently reported by Taqui Khan and Martell[108], is quite similar to oxalate oxidation. Two successive one-electron transfers to the metal ion, as indicated, convert the ascorbate monoanion to dehydro ascorbic acid. The final product has two less electrons than the original ligand and is a very poor electron donor, so that the metal chelate dissociates in solution. Thus the metal chelate ring is broken as a result of the oxidation reaction. Although the carbon–carbon bond is not ruptured, it is considerably weakened, since it is converted from a double to a single bond. The mechanism of oxidation of ascorbic acid by various iron chelates is similar to oxidation by the ferric ion[108], except that the rates are very much slower. As indicated in *Figure 20*, the second order rates (first order in substrate and first order in metal chelate) decrease rapidly as the stabilities of the metal chelates increase (and as the oxidation potentials of the Fe(II)L/Fe(III)L couples decrease). The observed rates seem to be dependent

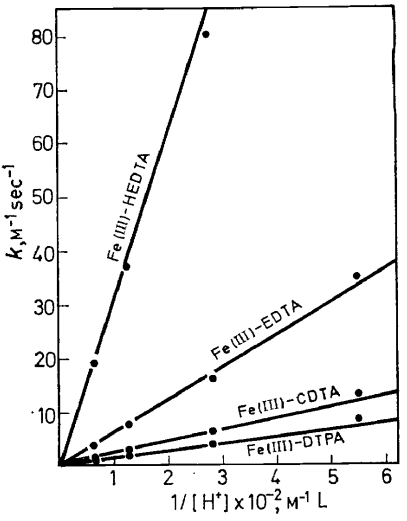


Figure 20. Dependence of rate on hydrogen ion concentration in the oxidation of ascorbic acid by Fe(III) chelates at 0·4°; ionic strength = 0·10 M (KNO_3)

on a steric effect, as well as on the redox potential of the metal chelate, indicating possible interference by the chelating ligand in the electron transfer step, which probably takes place in a mixed ligand chelate with the ascorbate anion.

Reactions of the type described above involving electron transfer to the metal ion, followed by dissociation of the metal chelate, may serve as the basis of catalytic systems in which the higher valence form of the metal ion is regenerated by reaction with an appropriate oxidizing agent. Thus the addition of chlorine to the manganese oxalate system regenerates Mn^{3+}, which then reacts again with the organic ligand, as follows[99]:

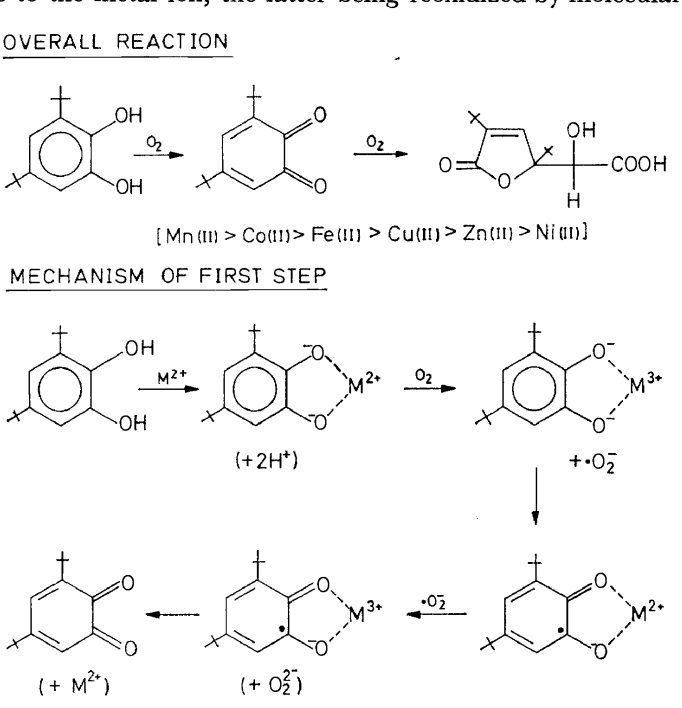
$$\begin{aligned} Mn^{3+} + C_2O_4^{2-} &\rightleftharpoons MnC_2O_4^+ \\ MnC_2O_4^+ &\rightarrow Mn^{2+} + C_2O_4^- \\ 2\,Mn^{2+} + Cl_2 &\rightarrow 2\,Mn^{3+} + 2\,Cl^- \\ Mn^{3+} + C_2O_4^- &\rightarrow Mn^{2+} + 2\,CO_2 \\ &\qquad \text{etc.} \end{aligned}$$

When the oxidant is permanganate, however, the Mn(II) is converted to Mn(III) in the form of the chelate, rather than as the free metal ion in solution, so that the reaction sequence is somewhat different[109, 110].

$$\begin{aligned} Mn^{2+} + C_2O_4^{2-} &\rightleftharpoons MnC_2O_4 \\ MnC_2O_4 + MnO_4^- &\rightarrow MnC_2O_4^+ + MnO_4^{2-} \\ MnC_2O_4^+ &\rightarrow Mn^{2+} + C_2O_4^- \end{aligned}$$

The catalytic effect of several metal ions on the oxidation of 3,5-ditertiarybutylpyrocatechol has been reported by Grinstead[111]. The mechanism

suggested (*Figure 21*) involves two successive electron transfers from the substrate to the metal ion, the latter being reoxidized by molecular oxygen



(Grinstead, 1964)
(Tyson and Martell, to be published)

Figure 21. Metal chelate catalysed oxidation of ditertiarybutyl catechol

without intermediate steps involving dissociation of the chelate. The intermediate Fe(III) chelate of the substrate free radical monoanion is of course indistinguishable from a Fe(IV) chelate of the reduced form of the ligand. It is interesting to note that of the metal ions listed in *Figure 21*, manganese has the highest catalytic activity. It therefore appears that the stability of the metal-substrate chelate is not the most important factor in determining the rate of reaction. The catalytic effect of the metal ion must be determined by the rate of the redox step with molecular oxygen, and/or the rate of the electron transfer between the metal ion and the substrate.

Another example of a metal–ligand redox reaction involving chelate ring rupture by two successive electron transfer steps is the Cr(III)-catalyzed oxidation of oxalate by Ce(IV) ions[112].

$$Cr(C_2O_4)_2^- + Ce^{4+} \rightarrow Cr(C_2O_4)_2^\circ + Ce^{3+}$$

$$Cr(C_2O_4)_2^\circ + Ce^{4+} \rightarrow CrC_2O_4^+ + 2\,CO_2 + Ce^{3+}$$

From the examples given above, it is seen that there is now considerable evidence that many metal chelate catalyzed oxidation reactions occur via two successive electron transfers from the substrate through the metal ion to the appropriate electron acceptor. Thus the metal ion seems to act as a

conductor for the transfer of electrons from the chelated substrate to the oxidant.

With a single-electron oxidant the mechanism must correspond to the examples given above. With a two-electron acceptor such as oxygen or hydrogen peroxide, however, an alternative mechanism is possible. At the time of electron transfer the oxygen is coordinated to the metal ion, probably in the same manner by which oxygen is bound in oxygen-carrying coordination compounds. After transfer of the first electron the oxygen should be a better donor, and may remain coordinated until the second electron transfer step that converts it to a peroxide. Thus a concerted or sequential two electron transfer from reductant to oxidant through the metal ion becomes possible. An example of this type of reaction is given in the next section.

(b) Mixed ligand complex formation with oxidant

The recent kinetic studies of Taqui Khan and Martell[113] on the metal ion-catalyzed oxidation of ascorbic acid by molecular oxygen provides an interesting example of metal chelate catalysis in which the metal ion serves as a bridging group for electron transfer from reducing agent to oxidant. The proposed reaction sequence which is based on first order dependence of the rate on the Cu^{2+} or Fe^{3+} ion, on the monoanion of the substrate, and on the concentration of molecular oxygen, involves pre-equilibrium formation of a mixed ligand chelate containing these three components:

$$M^{n+} + HA^- \rightleftharpoons MHA^{(n-1)+}$$

$$MHA^{(n-1)+} + O_2 \rightleftharpoons MHA(O_2)^{(n-1)+}$$

$$MHA(O_2)^{(n-1)+} \xrightarrow{\text{slow}} M^{n+}(HA\cdot)(O_2^{-})$$

$$M^{n+}(HA\cdot)(O_2^{-}) \xrightarrow{\text{fast}} M^{n+} + HA\cdot + O_2^{-}$$

$$HA\cdot + O_2^{-} \xrightarrow{\text{fast}} HO_2^{-} + A$$

$$HA\cdot + M^{n+} \xrightarrow{\text{fast}} M^{(n-1)+} + A + H^+$$

$$M^{(n-1)+} + O_2^{-} \xrightarrow{\text{fast}} M^{n+} + O_2^{2-}$$

Alternative Reaction Sequence

$$M^{n+}(HA\cdot)(O_2^{-}) \xrightarrow{\text{fast}} M^{n+}(A)(HO_2^{-}) \xrightarrow{\text{fast}} M^{n+} + A + HO_2^{-}$$

According to this mechanism, the rate-determining step occurs in the mixed ligand chelate in which the ascorbate monoanion and the oxygen molecule are simultaneously coordinated to the metal ion. After the first electron transfer occurs, the mixed ligand chelate may dissociate, as indicated, and the second electron transfer would then take place in a series of fast free radical reactions of the type illustrated in the proposed reaction scheme. On the other hand the alternative reaction scheme, by which the mixed ligand chelate holds together until the second electron transfer has occurred, seems more reasonable, for the reasons given above in the previous section.

Structural formulae for the species involved in the proposed mechanism through the first electron transfer step are shown in *Figure 22.* The more reasonable alternative mechanism involving two successive electron transfers in the mixed ligand chelate would differ only in the addition of a second

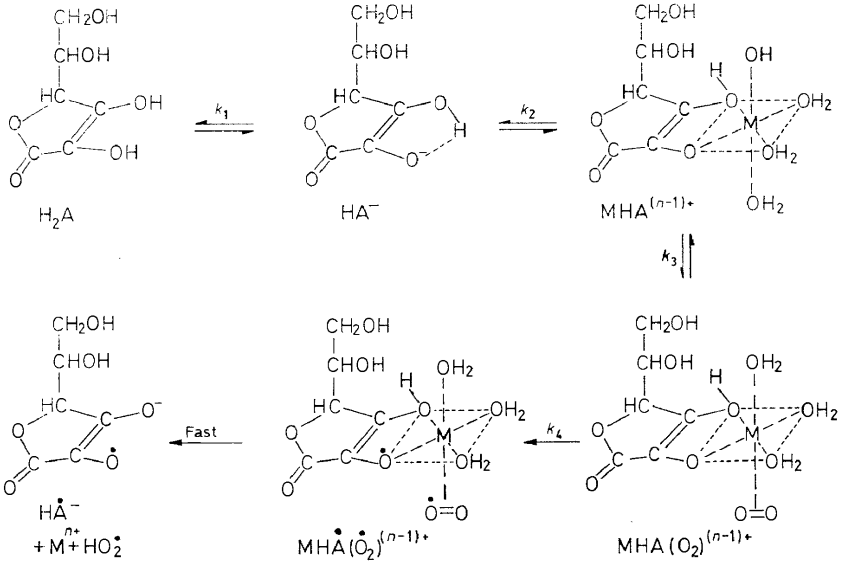


Figure 22. Mechanism of metal ion-catalysed oxidation of ascorbic acid (Path II)

electron transfer step with the eventual formation of dehydroascorbic acid and peroxide before dissociation of the metal chelate.

The metal ion-catalyzed oxidation of pyrocatechols (e.g., ditertiarybutylpyrocatechol described above) by molecular oxygen may also take place by a mechanism similar to that proposed for metal ion-catalyzed oxidation of ascorbic acid. Thus far, however, there is no experimental evidence for or against the formation of an intermediate oxygen complex in the oxidation of pyrocatechols.

Copper(II) catalysis of the oxidation of ethylenediamine and glycine by hydrogen peroxide has been suggested by Anbar[107] to involve Cu(III) chelate intermediates, which then undergo electron transfer from the ligand to the metal ion. Completion of the oxidation, in which the amino group is converted to an aldehyde group, was presumed to occur via subsequent free radical reactions in solution. Here, again, however, it seems that both of the successive electron transfers required to convert reactants to products could very well take place without dissociation of the intermediate mixed ligand chelate, as is indicated in *Figure 23.* The essential feature of this mechanism is the function of the metal ion in holding together the substrate and oxidant species during the rate determining electron transfer step(s). The stepwise removal of protons and electrons from the ligand may occur as concerted reactions, or in an order different from the one illustrated in *Figure 23.* A similar reaction described by Fallab[114], the Cu(II)-catalysed autoxidation of phenylenediamine, has been suggested by Anbar[107] to

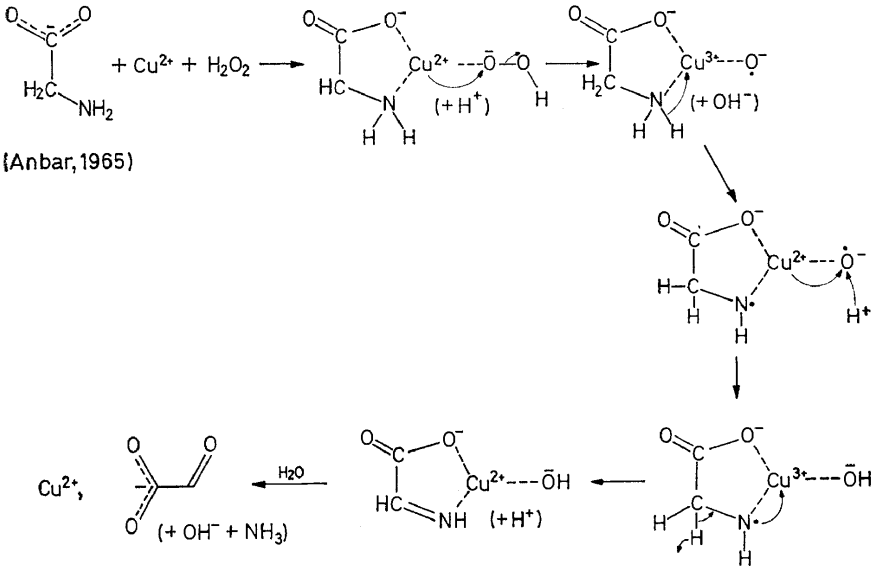


Figure 23. Oxidation catalysis with secondary ligand as oxidant

involve a mechanism similar to that suggested in *Figure 23.* It has been pointed out by Halpern[115] that a mechanism involving hydride ion transfer to Cu(II) would also satisfy the experimental data on Cu(II) catalysis of glycine and ethylenediamine oxidation, and should be considered a reasonable alternative to the proposed mechanisms.

(c) Rearrangements and internal redox reactions of the ligand

The metal ion-catalyzed reactions of Schiff bases formed from pyridoxal and amino acids, reported by Snell, Metzler, *et al.*[90–94] provide interesting examples of the breaking of metal chelate rings without change in the oxidation state of the metal ions. In the presence of Cu(II), Fe(III) and Al(III), the Schiff bases formed from alpha amino acids and pyridoxal undergo isomerization and internal ligand redox reactions which lead to the rupture of carbon–carbon bonds or elimination reactions.

As explained above (*Figure 18*), the metal-catalyzed displacement of a proton from the aldimine chelate results in the formation of a carbanion which then may undergo proton addition, resulting in transamination and proton exchange reactions of the ligand. The electron excess of the carbanion may also be relieved, as indicated, by the elimination of an electronegative group X, as an anion, X^-. In these three reactions (transamination, exchange and elimination), metal chelate rings are not broken, but are somewhat modified, and chemical bonds are rearranged.

Under the reaction conditions employed the electron attraction effect of the metal ion may produce the rupture of a carbon–carbon bond rather than the rupture of a carbon-hydrogen bond, giving rise to decarboxylation, or to the breaking off of the side chain of the amino acid. Both of these reactions are illustrated in *Figure 24.*

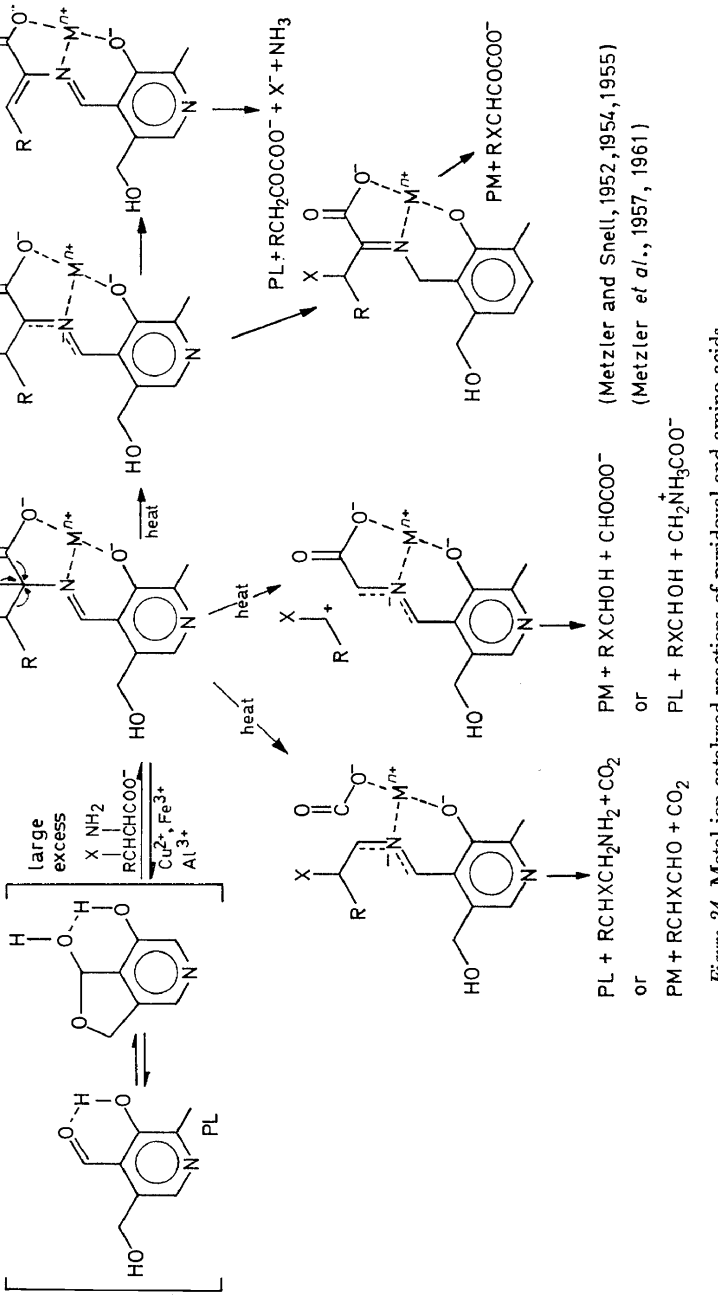


Figure 24. Metal ion-catalysed reactions of pyridoxal and amino acids

The considerable diversity of effects shown in *Figure 24* illustrates the versatility and complexity of metal chelate catalysis that may take place in a single ligand. With the exception of the transamination reaction itself, no mechanistic studies have been made on the several reactions shown in *Figure 24*. It is apparent that much more basic information is needed to clarify the nature of these reactions, and the stepwise chemical transformations that take place.

IV. REACTIONS IN WHICH THE METAL CHELATE RING IS NOT ALTERED

Although the title of this classification of metal chelate-catalyzed reactions may seem somewhat ambiguous, it includes some very interesting and important reaction types. Thus the masking of reactivity (i.e., negative catalysis) makes possible reactions at some remote part of the ligand without influencing the donor groups coordinated to the metal ion. In a second reaction type in which metal chelate rings are not altered the catalytic species is a metal chelate having free (aquo) positions on the metal ion through which the reaction with a substrate takes place. In this case the chelating ligand acts as a carrier for the metal ion, and catalysis occurs through the formation of a mixed ligand chelate compound. In still more complex systems, metal chelate catalysis may occur in a chelate which is altered and dissociates as the result of the reaction promoted by the metal ion. The original chelate may then be regenerated to produce a continuous series of reaction cycles, while the metal chelate is present in a steady state concentration. Under these conditions the metal chelate would be considered as a true catalyst since it would not be permanently altered as a result of the reaction taking place.

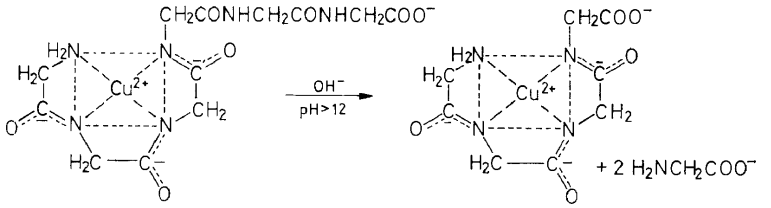
Examples of each of these reaction types are given below.

(a) Masking of reactivity

The masking of reactivity of coordinated donor groups of a chelated ligand may occur through direct electronic (i.e., ionic) interaction with the metal ion, through a change in the redox potential of the ligand, and through steric effects resulting directly from coordination of the ligand[116]. The observed changes of reactivity are usually due to a combination of these effects.

A striking example of the change of reactivity toward nucleophilic reagents that can occur on coordination is the protection of peptides against hydrolysis by coordination with Cu(II). An example of this masking effect, recently reported by Freeman and coworkers[117], is illustrated in *Figure 25*. At the high pH prevailing in solution, any free ligand is very rapidly hydrolyzed, as well as all the peptide residues of the coordinated ligand, except those that are coordinated to the metal ion through the peptide nitrogen. The nucleophilic reactivity of all coordinated peptide linkages is very greatly reduced when peptide protons are displaced by the metal ion. The resulting negative charge on each coordinated peptide linkage repels attack by nucleophilic reagents such as the hydroxide ion. This masking

PEPTIDE HYDROLYSIS



Cu(II)-hexaglycine chelate (Freeman *et al.*, 1967)

Cu(II)-Tetraglycine chelate

Figure 25. Ligand stabilization (masking) by chelate formation

effect may be considered primarily electronic in nature, although it is possible that there is also some steric inhibition of nucleophilic attack.

A similar example of hydrolytic cleavage of the terminal amino group on the copper(II) chelate of a peptide derivative has been reported by Nakahara *et al.*[118]. The ligand in this case is the salicylaldehyde Schiff base of tetraglycine. When the 1:1 Cu(II) chelate is formed, the ligand loses hydrogen ions from the phenolic, carboxyl, and two peptide protons to give the complex, $CuH_{-2}L^{2-}$. The uncoordinated peptide linkage does not have a negative charge and is susceptible to hydrolysis, resulting in facile cleavage of the glycine residue most remote from the Schiff base nitrogen.

Many reactions of remote functional groups of metal chelates of alpha amino acids have been reported. Thus ornithine is readily converted to

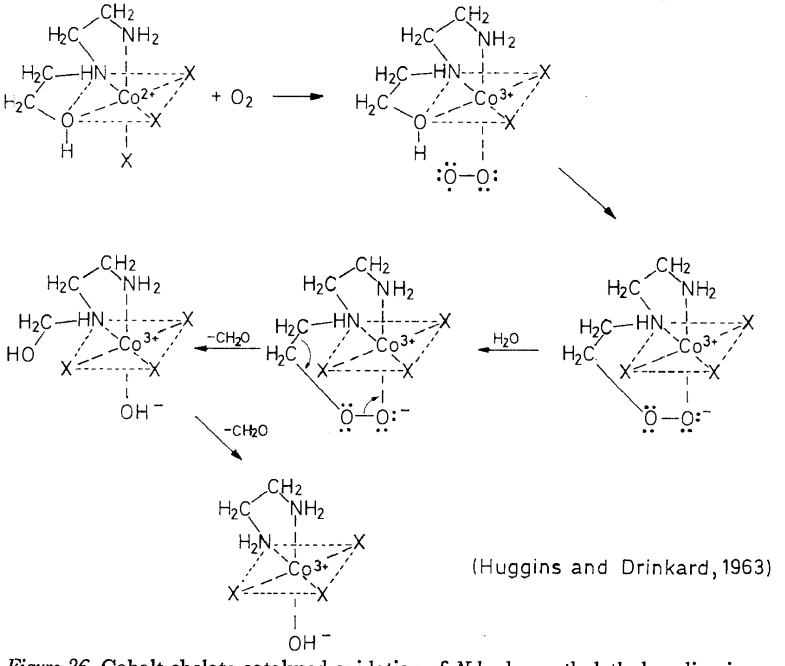


Figure 26. Cobalt chelate catalysed oxidation of *N*-hydroxyethylethylenediamine

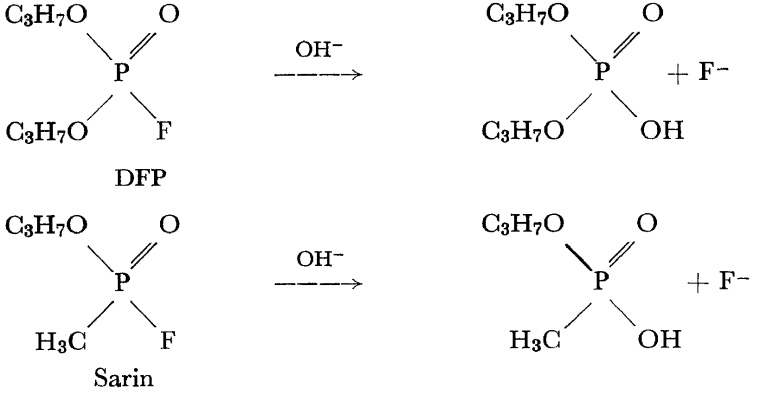
citrulline when combined with Cu(II) through the carboxylate and alpha amino groups, by reaction of the uncoordinated terminal amino group with urea[119–121]. A similar reaction with guanidine (or *o*-methylurea) yields arginine[122]. In the same manner free amino groups of Cu(II) chelates of alpha amino dicarboxylic acids may be selectively esterified[116].

The electronic effect of a metal ion in rendering a chelated ligand less susceptible to electrophilic attack provides some protection against oxidation of the coordinated groups of the ligand. Thus the free hydroxyethyl group of the *N*-hydroxyethylethylenediaminecobalt(III) ion may be selectively oxidized without interfering with the coordinated ethylenediamine residue, as is indicated in *Figure 26*. The mechanism of oxidation suggested by Huggins and Drinkard[123] is illustrated in *Figure 26*. More recently Anbar[107] has suggested an alternative mechanism consisting of oxidation of the cobalt(III) chelate to the cobalt(IV) state, followed by abstraction of an alpha proton, in the manner indicated above for the Cu(II)-catalyzed oxidation of ethylenediamine and glycine.

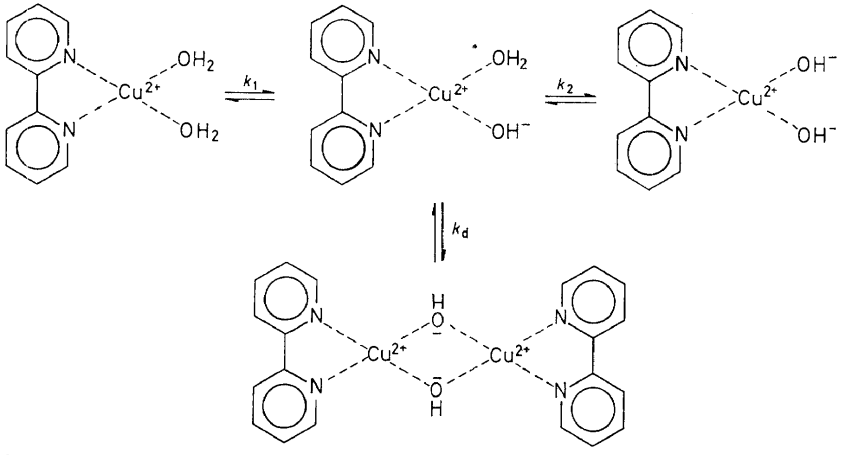
(b) Chelating ligand as a carrier for the metal ion

If a chelating ligand combines with a metal ion without displacing all of the coordinated water molecules, the resulting chelate may be stabilized against extensive hydrolysis and polymerization at high pH, without losing the ability to function as a Lewis acid in the catalysis of certain reactions. It is apparent that the interaction of a metal ion with a substrate is always decreased by coordination with a ligand that binds the metal sufficiently strongly to protect it aginst hydrolysis and precipitation. When high pH is required for the reaction as in the examples given below, the aquo metal ion cannot be employed as a catalyst. Under such conditions, however, a partially-chelated metal ion may be quite effective as a catalyst.

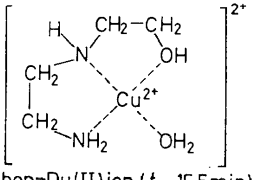
1. *Solvolysis by partially chelated metal ions.* Certain metal chelate compounds, in which the metal ion has considerable residual coordinating tendencies, are catalysts for the hydrolysis of fluorophosphates, such as the nerve gases diisopropylphosphorofluoridate (DFP), and isopropylmethylphosphonofluoridate (Sarin). These substances hydrolyze extremely slowly in water, but more rapidly at high pH, in accordance with the following reactions:



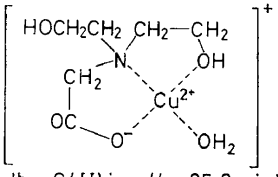
The catalytic effects of Cu(II) chelates of α-amino acids, α,α′-dipyridyl L-histidine, *o*-phenanthroline, and ethylenediamine on the hydrolysis of DFP were first reported by Wagner Jauregg *et al.*[124]. Further studies on the catalytic effects towards DFP hydrolysis of the Cu(II) chelates of ethylenediamine, α,α′-dipyridyl, and *o*-phenanthroline were described by Ryland *et al.*[125]. In these studies it was demonstrated that the 1.1 Cu(II)-dipyridyl catalyst exists as an equilibrium system involving mononuclear and binuclear species.



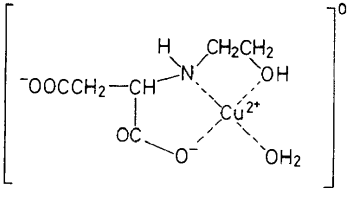
The catalytic effects of a wide variety of metal chelates on Sarin hydrolysis was reported by Courtney *et al.*[126]. Examples of the influence of structure and charge of the catalyst on the observed first order hydrolysis rate constants are indicated by the following half times of reaction for 1:1 Cu(II) chelates of the ligands, *N*-hydroxyethylethylenediamine (hen), *N*,*N*-dihydroxyethylglycine (dhg), *N*-hydroxyethylaspartate (hasp), and *N*-hydroxyethyliminodiacetic acid (himda):



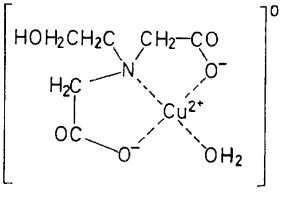
hen-Du(II) ion ($t_{1/2}$=15·5 min)



dhg-C(II) ion ($t_{1/2}$=25·0 min)



hasp-Cu(II) ion ($t_{1/2}$=45 min)



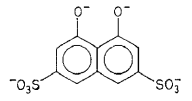
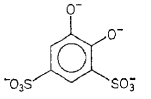
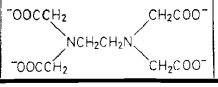
himda-Cu(II) ion ($t_{1/2}$=57 min)

The relative reaction rates listed above indicate that the best Cu(II) catalysts are those formed from neutral bidentate ligands. As the negative charge of

the ligand increases, and as the number of strongly-coordinating donor groups of the ligand increases, the catalytic activity decreases markedly. Thus it seems that neutral bidentate ligands form the most effective catalysts when coordinated to the Cu(II) ion.

Chelate compounds of a large number of metal ions were also investigated as catalysts for Sarin hydrolysis. Chelates of Zn(II), Cd(II), Mg(II), Ni(II), Pb(II), Fe(III), La(III), Cr(III), Ti(IV), and Sn(IV), formed with ligands that produce reasonably stable chelates at neutral pH have very little catalytic activity. On the other hand a number of chelates of oxo metal ions showed very high catalytic activity. Three of the most active of these chelates are listed in *Table 1.*

Table 1. Catalytic activities of oxometal chelates in the hydrolysis of sarin

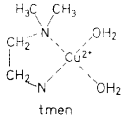
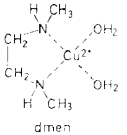
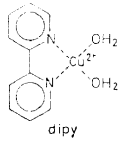
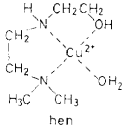
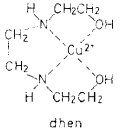
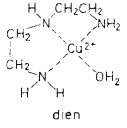
Metal Ion	*Ligand*	*Molar Concentrations of reactants* $\times 10^3$			$-Log\ [H^+]$	$t_{\frac{1}{2}}$ *(Min.)*
		Metal	*Ligand*	*Sarin*		
UO_2(VI)		0·41	0·82	1·3	7·00	4·4
MoO_2(VI)		0·96	0·96	0·91	7·10	7·5
ZrO(IV)		1·0	1·0	0·85	7·00	2·2

For a careful analysis of the reaction mechanism of such catalytic systems, it is necessary to relate the observed rates to specific species in solution, including the various forms of the metal chelate catalyst that might be present. By a detailed investigation of the metal chelate equilibria involved in catalytic systems containing 1:1 chelates of copper(II) and various ligands, Martell *et al.*[127–130] were able to assign catalytic effects for Sarin and DFP hydrolysis to specific metal chelate species in solution. These studies showed that the relative values of observed rates of hydrolysis do not reflect the relative catalytic effects of the reactive metal chelate species, because of varying tendencies to undergo side reactions that produce inactive forms. Thus the first order rate constants corresponding to the half times listed in *Table 2* are not proportional to the concentrations of the metal chelate compounds added to the reaction solutions as catalysts. Each of these Cu(II) chelates, except for the dien-Cu(II) chelate, was shown to be in equilibrium with a binuclear (olated) dihydroxo chelate which is catalytically inactive. Determination of the equilibrium constants listed in *Table 2* made possible comparisons of the variations of the observed catalytic effects with variations in concentration of the individual forms of the metal chelates present in solution. In this way it was found that in the pH range from 6–9 the 1:1

diaquo chelate is the reactive catalyst for both DFP and Sarin hydrolysis, in accordance with the following rate law:

$$k_{obs} = k_{CuL}[CuL][OH^-] + k_{OH}[OH^-] + k_{H_2O}$$

Table 2. Relative catalytic effects of some Cu(II) chelates of DFP hydrolysis (DFP = $4{\cdot}14 \times 10^{-3}$M Catalyst = $2{\cdot}07 \times 10^{-3}$M pH = 7·00 T = 25·3°)

	pK_1	pK_2	$\log K_d$	$\log K_{ML}$	$t_{1/2}$ (*min.*)
 tmen	8·0	9·8	3·9	7·2	15
 dmen	8·5		4·7	9·7	28
 dipy	8·0		5·3	17·85 ($k_1k_2k_3$)	23
 hen	7·3	9·3	2·2	10·0	91
 dhen	7·3		2·1	9·6	250
 dien	9·2			15·9	3000

where k_{obs} is the observed first order rate. The third order catalytic rate constant k_{CuL} is of course kinetically equivalent to a specific second order rate constant, k_{CuLOH}, since the concentration of the hydroxo chelate, CuLOH, is proportional to the product of the concentration of the diaquo chelate and the concentration of hydroxide ion. With this approach to the determination of the reactivities of catalytic species in solution, the specific rate constants listed in *Table 3* were obtained[128, 129].

The data in *Table 3* give a somewhat different picture on metal chelate catalysis than do the corresponding observed rates in *Table 2*. It is seen, for example, that the most effective catalyst for DFP hydrolysis is the diaquo Cu(II)–dipyridyl chelate. On the other hand this catalyst is in equilibrium with a relatively large proportion of the inactive binuclear species, so that it is less effective in solution than a somewhat less reactive catalyst that undergoes less polymerization such as the tmen-Cu(II) chelate.

Table 3. Specific third order catalytic rate constants for Cu(II)–chelate catalysis of DFP and Sarin hydrolysis

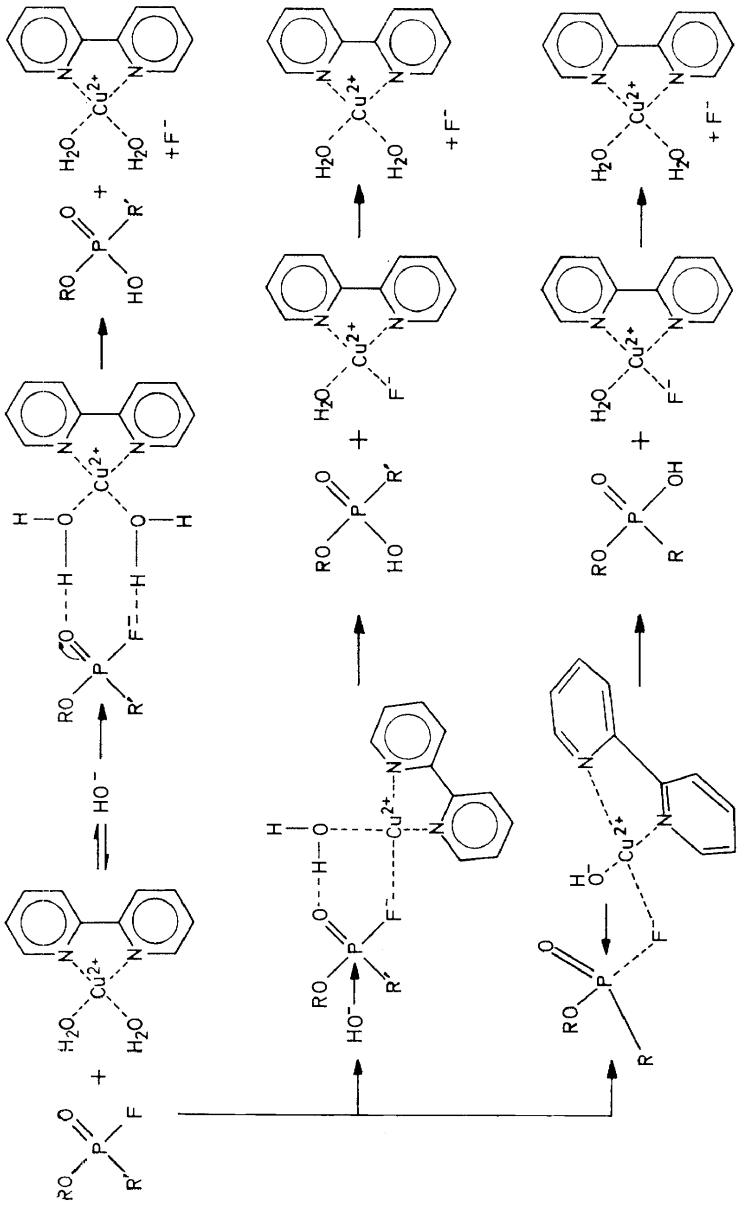
Ligand	*DFP Hydrolysis* (k_{ML}, M^{-2} sec^{-1}	*Sarin Hydrolysis* K_{ML}, M^{-2} sec^{-1})
tmen	$7{\cdot}0 \times 10^6$	$1{\cdot}0 \times 10^8$
dmen	$2{\cdot}3 \times 10^6$	$3{\cdot}2 \times 10^7$
dipy	$7{\cdot}4 \times 10^6$	$3{\cdot}1 \times 10^7$
o-phen	$4{\cdot}9 \times 10^6$	$1{\cdot}9 \times 10^7$
hen	$6{\cdot}4 \times 10^5$	$9{\cdot}3 \times 10^6$
dhen	$4{\cdot}0 \times 10^5$	$5{\cdot}2 \times 10^6$

The variations in relative catalytic activities toward DFP and Sarin hydrolysis listed in *Table 3* show that steric effects are important as well as ionic interaction of the substrate with the metal ion. These steric effects must arise from ligand–ligand interactions in the mixed ligand chelates formed as reactive intermediates, in which the metal ion is coordinated simultaneously to both substrate and metal chelate carrier.

Possible reaction mechanisms for the metal–chelate catalyzed hydrolysis of Sarin, DFP, and other fluorophosphates are illustrated in *Figure 27*.

The experimental data clearly show that the activated complex contains the metal chelate, substrate, and hydroxide ion. These species may react by hydroxide ion attack on a mixed ligand chelate formed by combination of the substrate with the metal chelate in a pre-equilibrium step. As indicated in *Figure 27*, the substrate may be directly coordinated to the metal ion in the mixed ligand chelate, or may be hydrogen bonded to the metal ion through one or more molecules of solvent. The rate determining step probably involves the breaking of the fluorine–phosphorus bond and coordination of the fluoride ion with Cu(II), to give an intermediate fluoro complex which subsequently dissociates to regenerate the original metal chelate catalyst.

The third possible reaction sequence shown in *Figure 27* involves pre-equilibrium dissociation of a proton from the aquo Cu(II) chelate, followed by transfer of a hydroxide ion to the phosphorus atom, and reverse transfer of a fluoride ion to the Cu(II) atom, through a concerted "push-pull" type of mechanism, This reaction sequence is kinetically equivalent to the others shown in *Figure 27*, and is suggested by the fact that metal chelates that have been found to have considerable catalytic reactivity in the hydrolysis of Sarin and DFP generally also undergo hydrolysis to hydroxo chelate species. This correlation is highly suggestive of a push–pull type mechanism involving a second order reaction between the hydroxocopper(II) chelate and the substrate. On the other hand, this tendency toward hydrolysis of the catalytically reactive chelates may merely be a consequence of the high



(Gustafson and Martell, 1962)
(Gustafson, Chaberek and Martell, 1963)

Figure 27. Metal chelate catalysed hydrolysis of Sarin and DFP

residual coordinating tendency of the metal ion required to achieve catalysis in the pH range needed for the hydrolysis of the fluorophosphate.

2. *Redox Catalysis. Metal Chelate-Catalyzed Oxidation of Ascorbic Acid.* Another reaction system in which a chelating agent acts as a carrier for the metal ion, and the metal chelate catalyst remains intact throughout the reaction cycle, is the metal chelate-catalyzed oxidation of ascorbic acid by molecular oxygen. *Figure 28* illustrates the variation of rate of oxidation of ascorbic

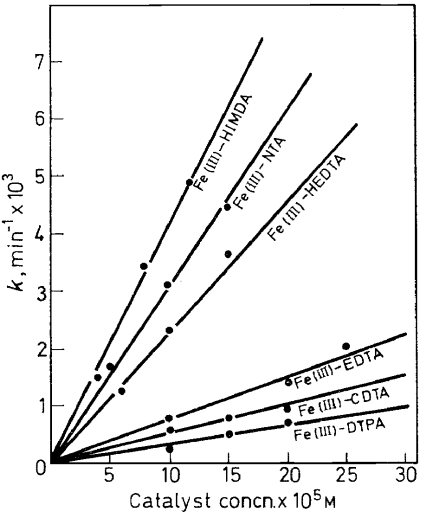


Figure 28. Dependence of the specific rate constants "*k*" on hydrogen ion concentration for Fe(III) chelate-catalysed oxidation of ascorbic acid at 25°; ionic strength = 0·10 M (KNO_3).

acid as a function of the concentrations of Fe(III) chelates, reported by Taqui Khan and Martell[131]. In contrast to the catalytic effects of copper(II) chelates on Sarin and DFP hydrolysis, described above, the catalytic rate constants are seen here to be directly proportional to the concentrations of the Fe(III) chelate compounds. Thus the reaction seems to involve straightforward catalysis by the normal metal chelate, with no appreciable concentrations of inactive forms of the metal chelate present. The rates of ascorbic acid oxidation were also found to be inversely proportional to hydrogen ion concentration, indicating the reactive form of the substrate to be the monoanionic form. The mechanism proposed to account for these facts involves pre-equilibrium formation of a mixed ligand chelate with the substrate, followed by a rate determining electron transfer, as is indicated below:

$$ML^{n+} + HA^- \rightleftharpoons ML(HA)^{(n-1)+}$$

$$ML(HA)^{(n-1)+} \xrightarrow{\text{slow}} ML^{(n-1)+} + HA\cdot$$

$$HA\cdot + O_2 \xrightarrow{\text{fast}} A + HO_2^{\cdot}$$

$$ML^{n+} + HA\cdot \xrightarrow{\text{fast}} ML^{(n-1)+} + A + H^+$$

$$ML^{(n-1)+} + O_2 \xrightarrow{\text{fast}} ML^{n+} + O_2^-$$

$$ML^{(n-1)+} + H_2O_2 \xrightarrow{\text{fast}} ML^{n+} + OH^- + OH\cdot$$

The redox reaction is pictured as occurring through a single electron transfer followed by dissociation of the reduced form of the metal chelate, and reoxidation by molecular oxygen in the body of the solution, thus regenerating the catalyst for another reaction cycle. The suggestions made for other metal-catalyzed redox systems described above, involving two successive transfers through the metal ion, probably do not apply in this case, since the metal ion oxidant can accept only one electron, and is well-shielded in the activated mixed ligand complex from attack by molecular oxygen. Thus it seems that the dissociation step after the first electron transfer is necessary in order to achieve contact between the metal ion (combined with the chelating ligand carrier) and molecular oxygen.

The data in *Figure 28* seem to fall into two different groups, catalysts of relatively low stability with high activity, and a less active group of catalysts consisting of chelates of considerably higher stability. It is probable that the more reactive group of metal chelates combine much more readily with the substrate forming a higher concentration of the activated complex. Thus it seems that two factors control the reaction rate: 1, the affinity of the metal chelate for the substrate; and 2, the oxidation potential of the metal in the activated complex. Rapid reoxidation of the metal chelate in solution is not rate determining.

It should be pointed out that alternative reaction mechanisms of the type proposed by Anbar[107], involving oxidation of Cu(II) and Fe(III) to Cu(III) and Fe(IV), respectively, are also possible for these systems. Prior oxidation of the metal ions in the form of their chelates, followed by electron transfer in a mixed ligand chelate type of activated complex is compatible with the experimental data.

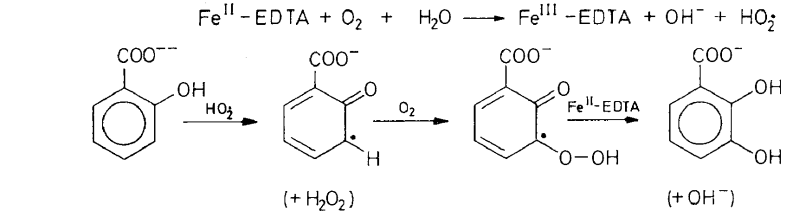
(c) Complex systems in which the metal chelate catalyst is regenerated

Perhaps the most interesting and complex chelate catalyst systems are those in which the metal ion forms a chelate with the substrate, which is then decomposed through an oxidation, solvolysis, or rearrangement reaction and the metal ion is subsequently transferred to a new substrate molecule or ion to continue the catalysis. Such systems may involve a chelating ligand as a carrier for the metal ion, and the substrate may itself be formed by the combination of two or more constituents in solution. The following are some interesting examples of these complex catalytic systems involving breakdown and regeneration of the metal chelates.

1. *Udenfriend's system.* The reaction system in which molecular oxygen simultaneously oxidizes a two-electron reducing agent and an organic substrate with an oxidizable metal chelate as a catalyst was first described by Udenfriend *et al.*[132–134]. Typical reactions result in the substitution of hydroxyl groups in aromatic rings, or the conversion of alkenes to alkene oxides. Suitable metal ions are Fe(II), Mn(II), Cu(II), and Co(II) combined

with an appropriate chelating ligand. A two-electron donor to keep the metal ion in the catalytically active reduced state must also be present.

A typical reaction mechanism for the system containing Fe(II), EDTA, ascorbic acid, and with salicylic acid as substrate[135], is illustrated in *Figure 29*. The reaction sequence is pictured as a free radical substitution of the aromatic ring by HO_2, generated by the single electron transfer from the



Regeneration of Fe(II)

Fe^{III}–EDTA + H_2A + OH^- → Fe^{II}–EDTA + HA· + H_2O
Fe^{III}–EDTA + HA· + OH^- → Fe^{II}–EDTA + A + H_2O
Fe^{III}–EDTA + H_2O_2 → Fe^{II}–EDTA + OH· + OH^-

Figure 29. Hydroxylation of salicylic acid by Udenfriend's system

Fe(II) chelate to oxygen. The Fe(II) chelate is regenerated by the two-electron reducing agent (ascorbic acid in this case). Stoichiometric quantities of ascorbic acid and oxygen are required in this reaction but the amount of metal chelate present can be relatively small.

The hydroxylating species in this system seems to be electrophilic in nature, and a preponderance of the substitution takes place *ortho* and *para* to the activating substituent(s) in the aromatic ring. For this reason non-free radical mechanisms now seem to be favoured for this type of reaction. An interesting mechanism recently suggested by Hamilton *et al.*[136, 137] is illustrated in *Figure 30*. Simultaneous attack of the Fe(II) ascorbate chelate, and the electron-donating substrate (an alkene) on molecular oxygen results in homolytic cleavage of the oxygen molecule. The alkene oxide

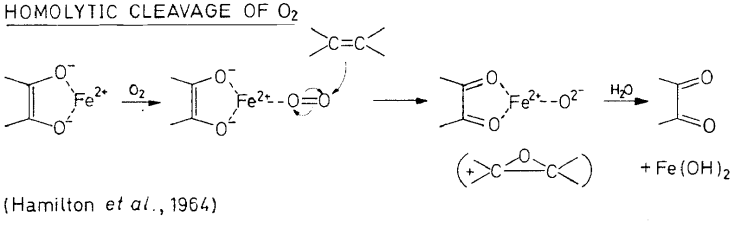


Figure 30. Proposed mechanisms for oxygen insertion in Udenfriend's system

and dehydroascorbic acid are formed, and Fe(II) is liberated, allowing continuation of the reaction sequence.

An alternative mechanism suggested by Taqui Khan and Martell[138], also illustrated in *Figure 30* involves an initial two-electron transfer from the ascorbate anion through the metal ion to molecular oxygen to form a mixed ligand chelate, containing a metal-peroxy bond. Under the influence of the metal ion the peroxide ligand cleaves heterolytically through an ionic mechanism when attacked by an electron-donating substrate.

From the mechanisms suggested it is apparent that the formation of a metal chelate intermediate is required to effect the observed catalysis, while a secondary chelating agent is also employed as a metal ion carrier and as a modifier of the oxidation potential of the metal ion.

2. *Oxidation by oxygen-carrying metal chelate compounds.* Recently, Beck and Gorog[139] reported that the oxidation of ascorbic acid is accelerated in the presence of the glycylglycine-cobalt(II) complex. The mechanism proposed[138] for this reaction involves preliminary formation of the oxygenated Co(II)-glycylglycine complex in aqueous solution, containing a 2:1 molar ratio of glycylglycino cobalt(II) and oxygen. This complex is isoelectronic with the corresponding μ-peroxoglycylglycinocobalt(III) chelate, illustrated in *Figure 31*. It is noted that there are two free *cis* coordination positions on each metal ion, which may provide suitable coordination sites for combination with the bidentate ascorbate anion. Thus electron transfer from the ascorbate anion to the metal ion would regenerate the original Co(II)–glycylglycine chelate and liberate the peroxide ion. The net reaction is

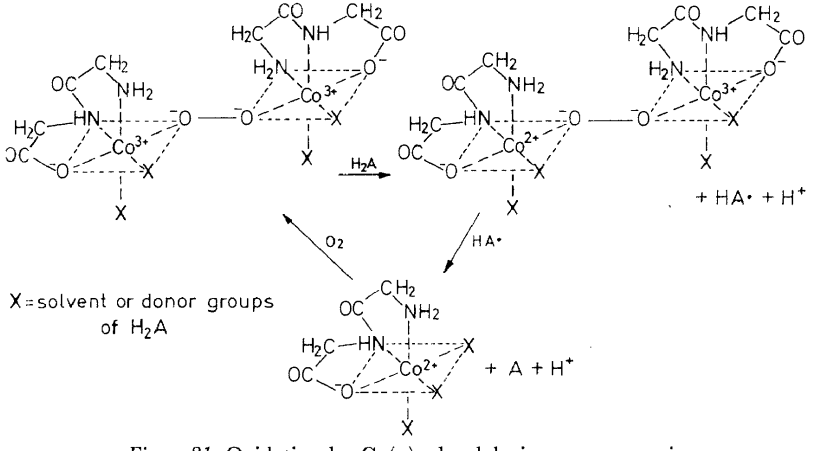


Figure 31. Oxidation by Co(II)–glycylglycine oxygen carrier

therefore reduction of oxygen to peroxide and oxidation of ascorbic acid to dehydroascorbic acid. The Co(II)–glycylglycine chelate that is regenerated is then free to combine with molecular oxygen to begin the next reaction cycle.

Although the reaction mechanism illustrated in *Figure 31* has not been demonstrated experimentally, it is in accord with the facts known thus far

about such systems, and demonstrates the interesting possibilities for catalysis by oxygen-carrying chelate systems.

3. *Metal Pyridoxal catalysis of transamination.* The metal ion-mediated reactions of Schiff bases of pyridoxal and amino acids, and of pyridoxamine and keto acids described above, provide the basis for a catalytic system in which relatively small amounts of the metal aldimine and metal ketimine chelates may catalyze the equilibration of relatively large amounts of two (or more) pairs of α-keto and α-amino acids. A mechanism described by Snell[140] for the catalytic conversion of an amino acid to a keto acid is illustrated in *Figure 32.* Reconversion of the pyridoxamine to pyridoxal by a second keto acid, R'COCOOH, results in redistribution of the compounds, $RCHNH_2COOH$, $R'CHNH_2COOH$, RCOCOOH, and R'COCOOH, in accordance with their relative activities in solution, in the presence of a relatively small amount of metal ion and pyridoxal/pyridoxamine as catalysts.

In catalytic systems involving Schiff bases of pyridoxal and pyridoxamine with amino and keto acids, it is interesting to compare the factors involved in metal ion and hydrogen ion catalysis, as illustrated in *Figure 33*[141]. The two parallel reaction sequences for hydrogen ion and metal ion catalysis are interesting since the data given in *Figure 18* show that metal ion catalysis is very much more rapid than hydrogen ion catalysis, even though the electronic interaction of the hydrogen ion with the Schiff base nitrogen

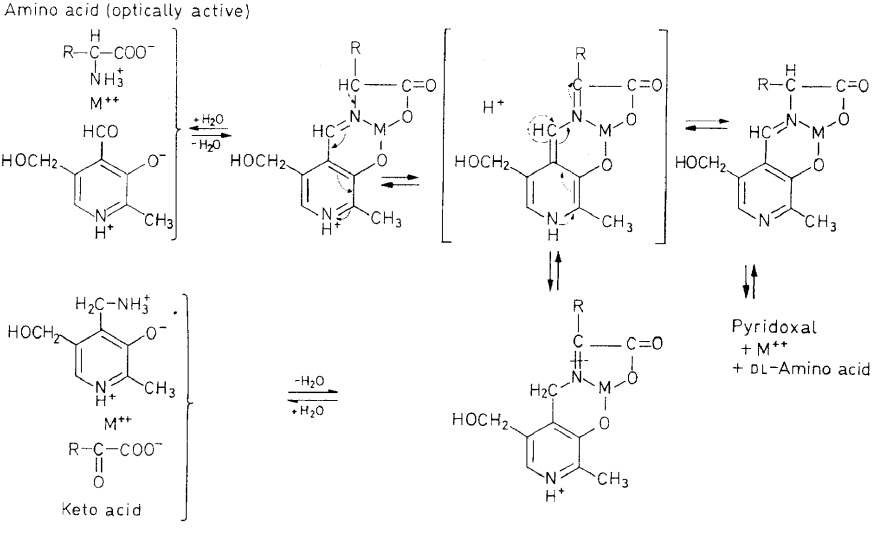


Figure 32. Mechanism for the catalytic conversion of an amino acid to a keto acid (Snell[140])

and adjacent groups must be much greater than that of a divalent metal ion. Apparently the metal ion is much more effective in stabilizing the negative (carbanionic) intermediate illustrated in *Figure 32.* The stabilization of this intermediate by delocalization of the negative charge would be favoured by metal chelate formation, since the ligand is terdentate and the metal ion would hold the intermediate much more rigidly than would the hydrogen ion. The relative catalytic effects of the metal ions, $Cu^{2+} > Ni^{2+} > Zn^{2+}$

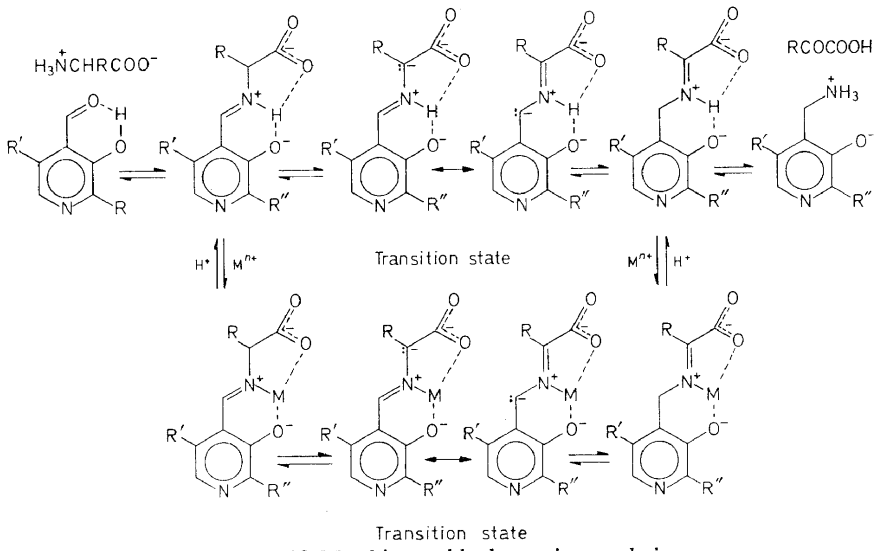


Figure 33. Metal ion and hydrogen ion catalysis

seems to correlate with the relative tendencies of these ions to form planar chelates. It is seen that a planar arrangement of the two chelate rings of the metal-Schiffs base would favour formation and stabilization of the carbanion intermediate.

4. *Model amine oxidase systems.* An interesting example of a metal chelate catalysed oxidation reaction in which oxidation of the ligand results in dissociation of the metal ion followed by regeneration of the original chelate is illustrated in *Figure 34.* The reaction mechanism shown is a modification of the suggestions of Hamilton and Revesz[142] for the Mn(II)-catalyzed oxidative deamination of amino acids in the presence of pyridoxal. Initial formation of the Mn(II) chelate of the Schiff base of pyridoxal and an α-amino acid results in the formation of the same type of metal ion-stabilized carbanion intermediate as is illustrated in *Figure 33.* An internal electron shift results in conversion of the amino acid moiety to a keto acid residue of a pyridoxamine Schiff base, which can then dissociate to the keto acid and the manganese chelate of a deprotonated pyridoxamine residue. Thus an internal redox reaction occurs in the ligand, involving oxidation of the amino acid part to a keto acid moiety, and reduction of the pyridine ring. At some point in the reaction sequence the ligand is oxidized by molecular oxygen, reacting through the metal ion. This may occur in the Schiff base chelate as illustrated, or oxidation may occur subsequently, after cleavage of the keto acid. The two-electron oxidation of the reduced pyridine ring results in regeneration of pyridoxal, and liberation of ammonia. Thus the net reaction involves the oxidation of an alpha amino acid by molecular oxygen to the corresponding keto acid and ammonia. Recent work on this system[143] has indicated the relative catalytic activities to follow the sequence $Mn^{2+} > Co^{2+} > Cu^{2+} \gg Ni^{2+} \sim 0$. Thus it is seen that the function of the metal ion cannot involve merely the transamination step [for which Cu(II) is

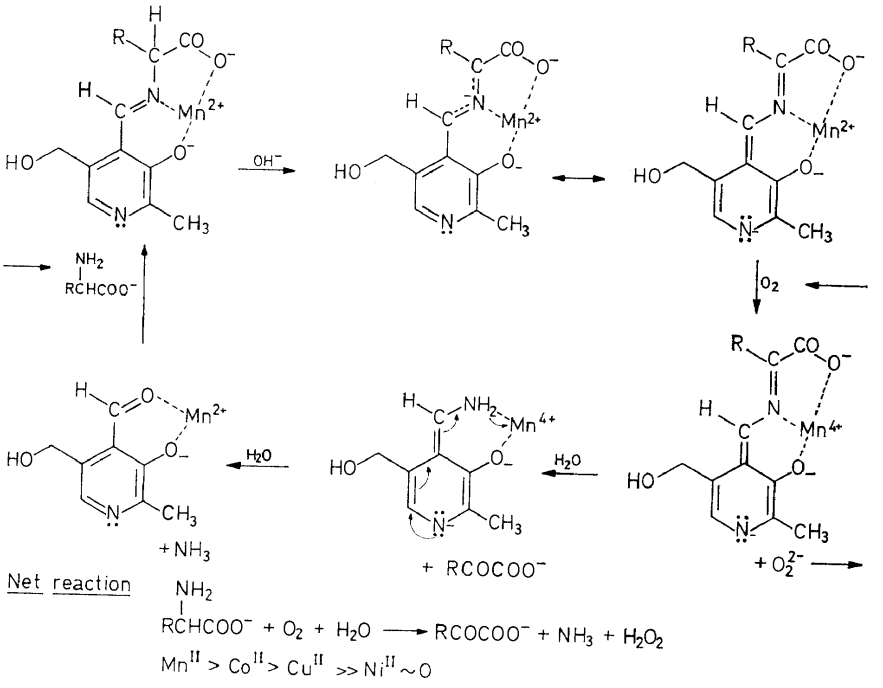


Figure 34. Metal ion and pyridoxal catalysis in the oxidative deamination of amino acids

shown above to be the best catalyst] but the ability of the metal ion to be oxidised to a higher oxidation state [which takes place most readily for Mn(II)] is also critically important in determining the catalytic effect.

CONCLUSIONS

The mechanisms suggested for the many types of metal ion-catalyzed and metal ion-promoted reactions described above are largely unproved. While these mechanisms are in accord with the limited facts available and hence are not pure speculation, extensive and detailed equilibrium and kinetic studies are needed in most cases to prove or disprove the interpretations given. These uncertainties, and the wide variety of reaction types involved, indicate almost unlimited possibilities for future research on catalytic effects involving metal chelate compounds.

When the general aspects of the various reaction types described above are considered, several important features of metal chelate catalysis seem to emerge. The following are some of the generalizations that may be made at this stage in the development of the field:

1. Metal chelate formation is an important driving force in metal ion-promotion of reactions of coordinated ligands. In many cases the transition state closely resembles the final metal chelate formed in the reaction. When this does not occur the equilibrium favouring the final metal chelate guides the reaction even though its formation is not kinetically favoured.

2. Metal ions promote nucleophilic attack on a chelated ligand. When formation of the metal chelate results in displacement of a proton or other positive group from the ligand, the negative charge of the ligand is increased, and the metal ion then catalyzes reactions of the ligand with electrophilic reagents.

3. When a metal ion catalyzes ligand reactions with nucleophilic reagents (when the ligand is made more positive by the metal ion) it decreases reactivity of the ligand toward electrophilic reagents. Similarly, the catalysis by metal ions of ligand reactions with electrophilic reagents involves corresponding negative catalysis with nucleophilic reagents. These negative catalytic effects offer many interesting applications in the field of organic synthesis.

4. Metal ions have many properties that make them highly effective in redox catalysis. Thus unusual oxidation states of the metal ion may be important as intermediates in electron transfer reactions. These unusual oxidation states may be much more readily attained when the metal is highly coordinated in a metal chelate compound than when it is present as a simple solvated ion in solution.

5. There now seems to be many instances of the mediation of redox reactions by metal ions in which the metal ion acts as a bridge for electron transfer from reductant to oxidant. This type of reaction also allows for the possibility of two successive electron transfers to form stable products, rather than decomposition to free radical intermediates after the first electron transfer step. Among the systems meeting the requirements for this type of reaction, the synthetic oxygen carriers would seem to offer considerable promise for future investigation.

6. Chelating ligands may act as carriers for metal ions at high pH where the metal ion itself does not exist. When the coordination positions of the metal are not completely covered by the chelate carrier, the metal ion may retain some activity as a Lewis acid. Reaction of such a metal chelate with an electron-donating substrate through mixed ligand chelate formation may greatly increase the reactivity of the substrate towards a base. Such reactions may be quite specific for metal chelates since they occur under conditions where proton catalysis and simple metal ion catalysis cannot occur.

7. Metal ion-catalyzed reactions frequently occur in dilute solution, or through intermediates that are present in trace amounts. Under these conditions the formation of metal chelate rings with the substrate greatly increases the catalytic effect, by greatly increasing the concentration of reactive intermediate in dilute solution.

8. A metal ion intermediate in a chemical reaction may function as a true catalyst, if the reaction conditions are such that it is efficiently regenerated after completion of each reaction cycle. Although only a small number of examples are now known, the design and study of catalyst systems of this type offer tremendous possibilities for future development.

It should be noted that efficient catalytic systems, in which metal

chelate intermediates are rapidly broken down and regenerated, must involve labile metal ions. Because of this lability, the reactive catalytic species may exist in many forms in solution, and careful, detailed equilibrium studies must first be carried out if the reaction kinetics are to be interpreted in terms of specific solution constituents. This type of approach —combining equilibrium and kinetic data—is required if meaningful mechanisms are to be deduced for complex catalytic systems containing chelates of labile metal ions.

References

1 A. E. Martell and M. Calvin, *Chemistry of the Metal Chelate Compounds*, Prentice Hall, Inc., Englewood Cliffs, N.J., 1952.
2 M. C. Thompson, D. H. Busch, J. A. Burke, Jr., D. C. Jicha, and M. I. Morris. *Adv. Chem. Ser.* No. 37, 125 (1963); *Chem. Eng. News* **39**, 57 (Sept. 17 1962).
3 F. A. Moser and A. I. Thomas, *Phthalocyanine Compounds*, Reinhold Publishing Corp., New York, 1963.
4 R. H. Ball, G. D. Dorough and M. Calvin. *J. Am. Chem. Soc.* **68**, 2278 (1946).
5 J. H. Priesthoff and C. V. Banks. *J. Am. Chem. Soc.* **76**, 937 (1954).
6 D. W. Thomas and A. E. Martell. *J. Am. Chem. Soc.* **78**, 1335 (1956).
7 E. B. Fleischer. *Inorg. Chem.* **1**, 493 (1962).
8 G. M. Badger, R. A. Jones and R. L. Laslett. *Austral. J. Chem.* **17**, 1028 (1964).
9 A. Eschenmoser. *Pure Appl. Chem.* **7**, 297 (1963).
10 R. L. N. Harris, A. W. Johnson and I. T. Kay. *Quarterly Reviews*, **20**, 211 (1966).
11 T. J. Hurley, M. A. Robinson and S. I. Trotz. *Inorg. Chem.* **6**, 389 (1967).
12 D. H. Williams and D. H. Busch. *Inorg. Chem.* **4**, 468 (1965).
13 G. A. Melson, and D. H. Busch. *Proc. Chem. Soc.* 223 (1963).
14 D. H. Busch. *Rec. Chem. Prog.* **25**, 107 (1964).
15 G. Hease and G. Ludwig. *Liebigs Ann.* **632**, 158 (1960).
16 M. P. Schubert. *J. Biol. Chem.* **114**, 341 (1936).
17 M. C. Thompson and D. H. Busch. *J. Am. Chem. Soc.* **84**, 1762 (1962).
18 M. C. Thompson and D. H. Busch. *J. Am. Chem. Soc.* **86**, 213 (1964).
19 N. F. Curtis. *J. Chem. Soc.* 4409 (1960).
20 N. F. Curtis and D. A. House. *Chem. & Ind.* **42**, 1708 (1961).
21 N. F. Curtis and M. M. Blight. *J. Chem. Soc.* 3016 (1962).
22 M. M. Blight and N. F. Curtis. *J. Chem. Soc.* 1204 (1962).
23 N. F. Curtis and Y. M. Curtis. *J. Chem. Soc.* 1653 (1966).
24 N. F. Curtis, Y. M. Curtis and H. K. Powell. *J. Chem. Soc.*, 1015 (1966).
25 H. Kroll. *J. Am. Chem. Soc* **74**, 2036 (1952).
26 M. L. Bender and B. W. Turnquest. *J. Am. Chem. Soc.* **77**, 4271 (1955).
27 M. D. Alexander and D. H. Busch. *J. Am. Chem. Soc.* **88**, 1130 (1966).
28 J. I. Hoppe and J. E. Prue. *J. Chem. Soc.* 1775 (1957).
29 A. Smith and B. Olin. *Z. physik. Chem.* **177**, 131 (1936).
30 E. Baumann and W. D. Mutterlein. *Chem. Ber.* **91**, 471 (1958).
31 E. Baumann and E. Nowotny. *Chem. Ber.* **81**, 451, 455, 463 (1948).
32 W. W. Butcher and F. H. Westheimer. *J. Am. Chem. Soc.* **77**, 2420 (1955).
33 R. J. Angelici and B. E. Leach. *J. Am. Chem. Soc.* **89**, 4605 (1967).
34 F. Lynen, E. Reichert and L. Ruff. *Liebigs Ann.* **574**, 14, 31 (1951).
35 J. R. Stern. *J. Biol. Chem.* **221**, 33 (1956).
36 L. Meriwether and F. H. Westheimer. *J. Am. Chem. Soc.* **78**, 5119 (1956).
37 J. P. Collman and D. A. Buckingham. *J. Am. Chem. Soc.* **85**, 3039 (1963).
38 Y. Murakami and A. E. Martell. *J. Am. Chem. Soc.*, **85**, 2119 (1964).
39 G. E. Mont and A. E. Martell. *J. Am. Chem. Soc.*, to be published.
40 M. L. Bender and J. M. Lawlor. *J. Am. Chem. Soc.* **85**, 3010 (1963).
41 Y. Murakami and M. Takagi, *Proceedings of the Xth International Conference on Coordination Chemistry*, Tokyo and Nikko, Japan; 12–16 September 1967, p. 205.
42 J. M. Lowenstein. *Biochem. J.* **70**, 222 (1958).
43 J. M. Lowenstein and M. N. Schatz. *J. Biol. Chem.* **236**, 305 (1961).
44 G. L. Eichhorn and J. C. Bailar, Jr. *J. Am. Chem. Soc.* **75**, 2905 (1953).
45 G. L. Eichhorn and I. M. Trachtenberg. *J. Am. Chem. Soc.* **76**, 5183 (1954).
46 D. H. Busch and J. C. Bailar, Jr. *J. Am. Chem. Soc.* **78**, 1137 (1956).
47 Y. Matsushima and A. E. Martell. *J. Am. Chem. Soc.* **89**, 1331 (1967).

48 A. E. Martell, and Y. Matsushima *Pyridoxal Catalysis: Enzymes and Model Systems*, IUB Symposium series Vol. 35, E. E. Snell, A. E. Braunstein, E. S. Severin and Yu. M. Torchinsky (Eds), Interscience Publishers, New York, N.Y. (1968).
49 G. L. Eichhorn and J. W. Dawes. *J. Am. Chem. Soc.* **76**, 5663 (1954).
50 E. Ochiai, H. Hirani and S. Makashima. *Polymer Letters*, **4**, 1003 (1966).
51 R. E. Rinehart, H. P. Smith, H. S. Witt and H. Romeyn. *J. Am. Chem. Soc.* **83**, 4864 (1961); **84**, 4145 (1962).
52 M. E. Pruitt and J. M. Baggett, U.S.Pat. 2 706 181 (1955).
53 A. E. Gurgiolo, Paper W7, 150th Meeting of the American Chemical Society, September, 1965, Atlantic City, N.J.
54 E. J. Corey. *Tetrahedron Letters* No. 2, 1 (1959).
55 G. Gee. *Trans. J. Plastics Inst.* **28**, 89 (1960).
56 R. O. Colclough, G. Gee and A. H. Jagger, Mezhdunarod Sympozium po Makromol. Khim., *Doklady* 1960, Sektsiya 1, 270–5.
57 E. J. Vandenberg. *J. Polymer Sci.* **47**, 486, 489 (1960).
58 R. E. Ireland and J. A. Marshall. *J. Am. Chem. Soc.* **81**, 2907 (1959).
59 M. Stiles. *J. Am. Chem. Soc.* **81**, 2598 (1959).
60 M. Stiles and H. L. Finkbeiner. *J. Am. Chem. Soc.* **81**, 505 (1959).
61 H. C. Longuet-Higgins and L. E. Orgel. *J. Chem. Soc.* **1969** (1956).
62 R. Criegee and G. Schroeder. *Angew. Chem.* **71**, 70 (1959).
63 W. Hubel and E. H. Braye. *J. Inorg. Nucl. Chem.* **10**, 250 (1959).
64 H. H. Freedman. *J. Am. Chem. Soc.* **83**, 2194 (1961).
65 M. E. Avram, E. Marica, and C. D. Nenitzescu. *Chem Ber.* **92**, 1088 (1959).
66 R. B. King, T. A. Manuel and F. G. A. Stone. *J. Inorg. Nucl. Chem.* **16**, 233 (1961).
67 D. St. C. Black. *Chem. Comm.*, 311 (1967).
68 J. D. Carr, R. A. Libby and D. W. Margerum. *Inorg. Chem.* **6**, 1083 (1967).
69 R. W. Hay. *J. Chem. Ed.* **42**, 413 (1965).
70 A. Kornberg, S. Ochoa and A. H. Mehler. *J. Biol. Chem.* **174**, 159 (1947).
71 J. F. Speck. *J. Biol. Chem.* **178**, 315 (1948).
72 R. W. Hay and E. Gelles. *J. Chem. Soc.* 3673 (1958).
73 E. Gelles and A. Salama. *J. Chem. Soc.* 3683, 3689 (1958).
74 J. E. Prue. *J. Chem. Soc.* 2331 (1952).
75 R. Steinberger and F. H. Westheimer. *J. Am. Chem. Soc.* **73**, 429 (1951).
76 R. G. Asperger and C. F. Liu. *Inorganic Chem.* **6**, 796 (1967).
77 D. A. Buckingham and A. M. Sargeson, Personal communication (1967).
78 S. Akabori, T. T. Otani, R. Marshall, M. Winitz, and J. P. Greenstein. *Arch. Biochem. Biophys.* **83**, 1 (1959).
79 M. Sato, K. Okawa, S. Akabori. *Bull. Chem. Soc., Japan* **30**, 937 (1957).
80 M. Murakami and K. Takahashi. *Bull. Chem. Soc. Japan* **32**, 308 (1959).
81 B. L. Horecker. *J. Cell. Comp. Physiol.* **54**, Supp. 1, 95 (1959).
82 K. Pederson. *Acta Chem. Scand.* **2**, 252, 385 (1948).
83 H. Reihlen, R. Illig and R. Wittig. *Ber. dtsch chem. Ges.* **58**, 12 (1925).
84 C. Djordjevic, J. Lewis and R. S. Nyholm. *Chem. and Ind.* 122 (1959).
85 R. W. Kluiber. *J. Am. Chem. Soc.* **82**, 4839 (1960).
86 J. P. Collman, R. A. Moss, S. D. Goldby and W. S. Trahanovsky. *Chem. and Ind.* 1213 (1960).
87 J. P. Collman, R. A. Moss, H. Maltz, and C. C. Heindel. *J. Am. Chem. Soc.* **83**, 531 (1961).
88 J. P. Collman, R. L. Marshall, W. L. Young, III, and S. D. Goldby. *Inorg. Chem.* **1**, 704 (1962).
89 J. P. Collman. *Advanc. Chem. Ser.* No. 37, **78**, 78 (1963).
90 D. E. Metzler and E. E. Snell. *J. Am. Chem. Soc.* **74**, 979 (1952).
91 D. E. Metzler, M. Ikawa and E. E. Snell. *J. Am. Chem. Soc.* **76**, 648 (1954).
92 D. E. Metzler and E. E. Snell. *J. Am. Chem. Soc.* **77**, 2431 (1955).
93 D. E. Metzler. *J. Am. Chem. Soc.* **79**, 485 (1957).
94 L. Davis, F. Roddy and D. E. Metzler. *J. Am. Chem. Soc.* **83**, 127 (1961).
95 D. E. Metzler, J. B. Longenecker and E. E. Snell. *J. Am. Chem. Soc.* **76**, 639 (1954).
96 D. E. Metzler, J. Olivard and E. E. Snell. *J. Am. Chem. Soc.* **76**, 644 (1954).
97 L. J. Nunez and G. L. Eichhorn. *J. Am. Chem. Soc.* **84**, 901 (1962).
98 I. M. Beatty and D. I. Magreth. *J. Am. Chem. Soc.* **82**, 4983 (1960).
99 H. Taube. *J. Am. Chem. Soc.* **69**, 1418 (1947).
100 H. Taube. *J. Am. Chem. Soc.* **70**, 1216 (1948).
101 F. R. Duke. *J. Am. Chem. Soc.* **69**, 2885 (1947).
102 F. R. Duke. *J. Am. Chem. Soc.* **73**, 5179 (1951).
103 F. R. Duke and A. A. Forist. *J. Am. Chem. Soc.* **71**, 2790 (1949).
104 G. G. Guilbault and W. J. McCurdy. *J. Phys. Chem.* **67**, 283 (1963).
105 M. Anbar, R. Munoz and P. J. Rona. *J. Phys. Chem.* **67**, 2708 (1963).
106 M. Anbar, S. Guttmann, H. Krinovitch and R. Munoz (to be published).

107 M. Anbar. *Adv. Chem. Ser.* **49**, 129 (1965).
108 M. M. Taqui Khan and A. E. Martell. *J. Am. Chem. Soc.* **89**, (1967).
109 S. J. Adler and R. M. Noyes. *J. Am. Chem. Soc.* **77**, 2036 (1955).
110 J. Malcolm and R. M. Noyes. *J. Am. Chem. Soc.* **74**, 2769 (1952).
111 R. R. Grinstead. *Biochemistry*, **3** 1308 (1964).
112 J. E. Teggins, M. T. Wang, and R. M. Milburn. *Adv. Chem. Ser.*, **37**, 226 (1963).
113 M. M. Taqui Khan and A. E. Martell. *J. Am. Chem. Soc.* **89**, 4176 (1967).
114 S. Fallab. *J. Inorg. Nucl. Chem.* **8**, 631 (1958).
115 J. Halpern, Discussion of paper by M. Anbar, *Adv. Chem. Ser.* **49**, 145 (1965).
116 M. M. Jones. *Werner Centennial, Adv. Chem. Ser.* 62 (1967).
117 R. H. Andreatta, H. C. Freeman, A. V. Robertson, and R. L. Sinclair, *Chem. Comm.* 203 (1967).
118 A. Nakahara, Y. Nakao, K. Sakurai, Transactions of Xth ICCC, Nikko, Japan, 1967.
119 A. C. Kurtz. *Am. J. Med. Sci.* **194**, 875 (1937).
120 A. C. Kurtz. *J. Biol. Chem.* **122**, 477 (1938).
121 A. C. Kurtz. *J. Biol. Chem.* **140**, 705 (1941).
122 F. Turba and K. H. Schuster. *Z. Physiol. Chem.* **283**, 27 (1948).
123 D. Huggins and W. C. Drinkard. *Adv. Chem. Ser.* **37**, 181 (1963).
124 T. Wagner-Jauregg, B. E. Hackley, Jr., T. A. Lies, O. O. Owens, and R. Proper. *J. Am. Chem. Soc.* **77**, 922 (1955).
125 L. B. Ryland, F. M. Fowkes, and G. S. Ronary, Paper No. 108, Division of Physical and Inorganic Chemistry, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., Sept. 11–16, 1955.
126 R. C. Courtney, R. L. Gustafson, S. J. Westerback, H. Hyytiainen, S. C. Chaberek, Jr., and A. E. Martell. *J. Am. Chem. Soc.* **79**, 3030 (1957).
127 A. E. Martell, R. Gustafson and S. Chaberek, *Advances in Catalysis*, Academic Press, New York, 1957, p. 319.
128 A. E. Martell. *Adv. Chem. Ser.*, **37**, 161 (1963).
129 R. L. Gustafson and A. E. Martell. *J. Am. Chem. Soc.* **84**, 2309 (1962).
130 R. L. Gustafson, S. Chaberek and A. E. Martell. *J. Am. Chem. Soc.* **85**, 598 (1963).
131 M. M. Taqui Khan and A. E. Martell. *J. Am. Chem. Soc.* **89**, 7104 (1967).
132 S. Udenfriend, C. T. Clark, J. Axelrod and B. B. Brodie. *Fed. Proc.* 11, 301 (1952).
133 S. Udenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie. *J. Biochem.* **208**, 731, 741 (1954).
134 H. Axelrod, S. Udenfriend, and B. B. Brodie. *J. Pharmocol. Expt. Therap.* **III**, 176 (1954).
135 R. R. Grinstead. *J. Am. Chem. Soc.* **82**, 3472 (1960).
136 G. A. Hamilton. *J. Am. Chem. Soc.* **87**, 2291 (1964).
137 G. A. Hamilton, R. J. Workman, and L. Woo. *J. Am. Chem. Soc.* **86**, 2291 (1964).
138 M. M. Taqui Khan and A. E. Martell, Symposium on Inorganic Biochemistry, 151st Meeting of the American Chemical Society, Pittsburgh, Pa., April, 1966, (to be published).
139 M. T. Beck and S. Gorog. *Acta Chem. Acad. Sci. Hung.* **29**, 401 (1961).
140 E. E. Snell. *Fed. Proc.* (*Suppl 10*) **20**, 81 (1961).
141 A. E. Martell, Proceedings of Symposium on Chemical and Biological Aspects of Pyridoxal Catalysis, Rome, 1962, Pergamon Press, 1963, p. 13.
142 G. A. Hamilton and A. Revesz. *J. Am. Chem. Soc.* **88**, 2069 (1966).
143 M. Haruta and A. E. Martell, to be published.