COMPREHENSIVE COORDINATION CHEMISTRY

The Synthesis, Reactions, Properties & Applications of Coordination Compounds

Editor-in-Chief: Sir Geoffrey Wilkinson, FRS

Executive Editors: Robert D. Gillard & Jon A. McCleverty



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COMPREHENSIVE COORDINATION CHEMISTRY

The Synthesis, Reactions, Properties & Applications of Coordination Compounds

Volume 6

Applications

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Preface

Since the appearance of water on the Earth, aqua complex ions of metals must have existed. The subsequent appearance of life depended on, and may even have resulted from, interaction of metal ions with organic molecules. Attempts to use consciously and to understand the metal-binding properties of what are now recognized as electron-donating molecules or anions (ligands) date from the development of analytical procedures for metals by Berzelius and his contemporaries. Typically, by 1897, Ostwald could point out, in his 'Scientific Foundations of Analytical Chemistry', the high stability of cyanomercurate(II) species and that 'notwithstanding the extremely poisonous character of its constituents, it exerts no appreciable poison effect'. By the late 19th century there were numerous examples of the complexing of metal ions, and the synthesis of the great variety of metal complexes that could be isolated and crystallized was being rapidly developed by chemists such as S. M. Jørgensen in Copenhagen. Attempts to understand the 'residual affinity' of metal ions for other molecules and anions culminated in the theories of Alfred Werner, although it is salutary to remember that his views were by no means universally accepted until the mid-1920s. The progress in studies of metal complex chemistry was rapid, perhaps partly because of the utility and economic importance of metal chemistry, but also because of the intrinsic interest of many of the compounds and the intellectual challenge of the structural problems to be solved.

If we define a coordination compound as the product of association of a Brönsted base with a Lewis acid, then there is an infinite variety of complexing systems. In this treatise we have made an arbitrary distinction between coordination compounds and organometallic compounds that have metal–carbon bonds. This division roughly corresponds to the distinction — which most but not all chemists would acknowledge as a real one — between the cobalt(III) ions $[Co(NH_3)_6]^{3+}$ and $[Co(\eta^5\text{-}C_5H_5)_2]^+$. Any species where the number of metal–carbon bonds is at least half the coordination number of the metal is deemed to be 'organometallic' and is outside the scope of our coverage; such compounds have been treated in detail in the companion work, 'Comprehensive Organometallic Chemistry'. It is a measure of the arbitrariness and overlap between the two areas that several chapters in the present work are by authors who also contributed to the organometallic volumes.

We have attempted to give a contemporary overview of the whole field which we hope will provide not only a convenient source of information but also ideas for further advances on the solid research base that has come from so much dedicated effort in laboratories all over the world.

The first volume describes general aspects of the field from history, through nomenclature, to a discussion of the current position of mechanistic and related studies. The binding of ligands according to donor atoms is then considered (Volume 2) and the coordination chemistry of the elements is treated (Volumes 3, 4 and 5) in the common order based on the Periodic Table. The sequence of treatment of complexes of particular ligands for each metal follows the order given in the discussion of parent ligands. Volume 6 considers the applications and importance of coordination chemistry in several areas (from industrial catalysis to photography, from geochemistry to medicine). Volume 7 contains cumulative indexes which will render the mass of information in these volumes even more accessible to users.

The chapters have been written by industrial and academic research workers from many countries, all actively engaged in the relevant areas, and we are exceedingly grateful for the arduous efforts that have made this treatise possible. They have our most sincere thanks and appreciation.

We wish to pay tribute to the memories of Professor Martin Nelson and Dr Tony Stephenson who died after completion of their manuscripts, and we wish to convey our deepest sympathies to their families. We are grateful to their collaborators for finalizing their contributions for publication.

Because of ill health and other factors beyond the editors' control, the manuscripts for the chapters on Phosphorus Ligands and Technetium were not available in time for publication. However, it is anticipated that the material for these chapters will appear in the journal *Polyhedron* in due course as Polyhedron Reports.

We should like to acknowledge the way in which the staff at the publisher, particularly Dr Colin Drayton and his dedicated editorial team, have supported the editors and authors in our

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We should also like to acknowledge the way in which the staff at the publisher, particularly Dr Colin Drayton and his dedicated editorial team, have supported the editors and authors in our endeavour to produce a work which correctly portrays the relevance and achievements of modern coordination chemistry.

We hope that users of these volumes will find them as full of novel information and as great a stimulus to new work as we believe them to be.

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Electrochemical Applications

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57.1 INTRODUCTION

This chapter will carefully differentiate situations in which coordination of metal ions assists in the achievement of specific electrochemical aims from experiments designed to study the electrochemistry of coordination compounds. (For information on the latter topic, see, particularly, Chapters 8.1–8.3). Two major areas have been selected for consideration: one almost classical, namely the electrodeposition of metals, the other of more recent origin, namely the modification of electrode surfaces.

The two areas specified will require the coverage of a wide range of chemistry. Although the basic principles of electroplating are well understood, and the role of coordination compounds in some plating baths well established, new work and new directions are discernible, particularly in relation to bath additives and their mode of action.

Work on the modification of electrode surfaces is of more recent origin, but the research has already gathered considerable momentum. Coordination compounds have not played a unique role in this development, but they have on occasion made important advances possible. Some authors believe that this work will influence the direction of electrochemistry for many years to come. It certainly has implications for electrocatalysis, electronic devices, visual display units and photoelectricity to mention but a few topical objectives which currently drive the research.

57.2 ELECTRODEPOSITION OF METALS

57.2.1 Electrochemical Cells

Within an electroplating bath the deposition of a metal from solution on to a solid substrate clearly involves the transport of charge across the solution–substrate interface. The solution will

be an electrolyte, *i.e.* a phase in which charge is carried by ions, and the solid substrate will generally be a metal electrode in which charge is carried by electronic conduction. The focus of interest is generally the electrode at which electrodeposition occurs; however, it is not possible to study that electrode–electrolyte interface in isolation since it must be linked to at least one other such interface to form an electrochemical cell.

Electrochemical cells may be one of two types. Should a current spontaneously flow on connecting the electrodes *via* a conductor, the cell is a galvanic cell. An electrolytic cell is one in which reactions occur when an external voltage greater than the reversible potential of the cell is applied. Simple examples involving copper are given in Figure 1. It is the electrolytic cell which is of interest in the electrodeposition of metals.



Figure 1 Examples of (a) a galvanic cell and (b) an electrolytic cell. Copper metal is the cathode in (a), but the anode in (b)

When a metal is immersed in a solution of an electrolyte, a potential difference is set up at the metal–solution interface; this is the electrode potential. When a metal dips into a solution of its own ions, some ions may leave the metal and enter the solution, while others will deposit on the metal from solution. Since the ions are charged, an electrical double layer is created at the metal–solution interface. The equilibrium potential difference between metal and solution is the Galvani potential. When ions are transferred from solution to deposit on the metal, the metal consititutes the positive side of the double layer and *vice versa*.

In practice, in order to assign a relative numerical value for an electrode potential, two electrodes are combined in an electrochemical cell and the potential of one electrode, the reference electrode, is assigned an arbitrary value. The standard hydrogen electrode (SHE; platinum black electrode contacting dihydrogen gas at 1 atm and hydrogen ions at unit activity) is assumed to have a potential of zero. Experimentally more convenient is the standard calomel electrode (SCE; $Hg|Hg_2Cl_2|KCl$ saturated in water), which has a potential of 0.242 V *vs.* the standard hydrogen electrode.

It is clear that the passage of charge across the electrode–solution interface may cause oxidation or reduction. Since the amount of chemical change is governed by Faraday's laws, such processes are termed faradaic. A link exists between the electrode potential, E, and the concentrations (properly activities) of compounds of the electrode process. In general

$$\mathrm{Ox} + ne^- \rightleftharpoons \mathrm{Red} \tag{1}$$

where Ox and Red are the oxidized and reduced forms, respectively; hence using the Nernst equation

$$E = E^\circ + RT/nF \ln(a_{\mathrm{Ox}}/a_{\mathrm{Red}}) \tag{2}$$

where R is the gas constant, F the faraday and a represents activity. At unit activities

$$E = E^\circ \tag{3}$$

where E° is the standard potential.

In the case where the reduced form is a metal M

$$\mathrm{M}^{n+} + ne \rightleftharpoons \mathrm{M} \tag{4}$$

Equation (2) may be rewritten as

$$E = E^\circ + RT/nF \ln a_{\mathrm{M}}^{n+} \tag{5}$$

Thus it follows that a change in the concentration of M^{n+} will influence E. To take a simple example

$$\mathrm{Co(s)} + \mathrm{Ni}^{2+}\mathrm{(aq)} = \mathrm{Co}^{2+}\mathrm{(aq)} + \mathrm{Ni(s)} \tag{6}$$

If both aquo ions are present in $M|M^{2+}(aq)$ half cells at 1 M concentration, nickel metal is deposited on connecting the half cells. However, if the concentration of $Co^{2+}(aq)$ were reduced to 0.01 M in the cobalt half cell, deposition of cobalt would occur. Thus a change in concentration of a factor

of ten has caused E to change by the order of the difference of the E° values for the two half cells (*i.e.* 0.03 V).

It is not appropriate in this chapter to tabulate quantities of electrochemical data since that required may be obtained from texts on electrodeposition.[1,2] However, a brief mention of sign conventions must be made since, particularly in the early literature, confusion can arise. Two conventions have been used: the 'European' and the 'American'.[3] It is sometimes erroneously stated that the conventions differ only in sign; however, the real difference lies in the distinction between the potential of an actual electrode and the EMF of a half cell reaction.

The European convention assigns the sign (positive or negative) which the electrode would assume when immersed in a solution of its own ions. Thus a zinc electrode in a solution of $Zn^{2+}(aq)$ would assume a negative potential and E° is -0.763 V.

From a thermodynamic viewpoint the entry of zinc ions from the electrode to the solution is a spontaneous process in the presence of acid, hence

$$\Delta G^\circ = -nFE^\circ \tag{7}$$

The American convention would assign a positive value to E° for the $Zn|Zn^{2+}(aq)$ half cell written as an oxidation, *but* a negative sign if written as a reduction. It is seen that the European convention refers to the invariant electrostatic potential of the electrode with respect to the SHE, whereas the American convention relates to the thermodynamic Gibbs' free energy which is sensitive to the direction of the cell reaction.

IUPAC recommends that 'electrode potential' be reserved for the European convention, whereas the EMF of a half cell is dealt with *via* the American convention.

The predictive value of standard electrode potentials is nicely illustrated following Bard and Faulkner (an excellent source of fundamental theory) in Figure 2.[4] As the potential of the Pt or Hg electrode is moved from its equilibrium (zero current) value to more negative potentials, the species of more positive E° should be reduced first. This prediction is verified for the Pt electrode, but Cr^{3+} is reduced before H^+ for the Hg electrode.

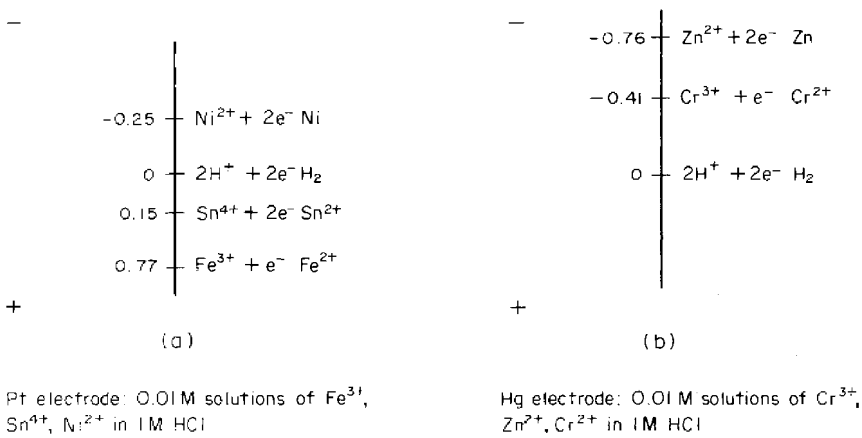


Figure 2

As is often the case in chemistry, it must be recognized that for real processes kinetic as well as thermodynamic factors must be considered.

57.2.2 Overvoltage and Polarization

The equilibrium at an electrode is dynamic, the potential determining ions moving in opposite directions at equal rates. If the process is reversible, the ions move smoothly from one phase to the other *via* the phase boundary and perform no work. The electrode potential remains constant and independent of current.

Kinetic factors may induce a variation of electrode potential with current; the difference between this potential and the thermodynamic equilibrium potential is known as the *overvoltage* and the electrode is said to be *polarized*. In a plating bath this change of potential can be attributed to the reduced concentration of depositing ions in the double layer which reduces the rate of transfer to the electrode, but the dissolution rate from the metal increases. Since the balance of these rates determines the electrode potential, a negative shift in the value occurs: the concentration polarization (η_{conc}). Anodic effects are similar but in the opposite direction.

Other contributions to the polarization are activation polarizations (η_{act}) caused by inhibition of the passage of ions through the phase boundary which may arise in the discharge mechanism. Films on the electrode may also contribute (*e.g.* oxide, metal already deposited, impurity) by offering a resistance to current flow differing from the bath resistance (ohmic polarization, η_{ohm}). Hence the observed overvoltage is given by

$$E - E_{equilibrium} = (\eta_{conc} + \eta_{act} + \eta_{ohm})\,\text{ANODE} + (\eta_{conc} + \eta_{act} + \eta_{ohm})\,\text{CATHODE} + A \quad (8)$$

where A represents the ohmic term for the bulk bath. Quite commonly there is an overvoltage for hydrogen discharge, as in the example given in Figure 2.

Current–potential curves obtained under steady state conditions are called polarization curves. If two or more faradaic processes occur at the electrode, the fraction of current (i_r) driving the rth process is the *instantaneous current efficiency*. Over a period of operating time the fraction of the total number of coulombs used in the rth process (Q_R) is related to the *overall current efficiency* of that process (OCE), *i.e.*

$$\text{OCE} = Q_R/Q_{total} \quad (9)$$

Should this approach 100%, only one electrode process occurs.

57.2.3 Role of Coordination Compounds

The majority of commercial electroplating involves an aqueous medium; hence, depending on the pH of the solution, the metal ions will be present in the bath as aquo or hydroxo complexes. In many cases another complexing agent, usually cyanide, is added. Such baths are operated under alkaline conditions to prevent the release of HCN. The choice of a particular bath composition is determined by technical factors.Thus, for example, zinc–alkaline cyanide baths have an excellent macroscopic *throwing power*, that is the ability to produce a uniform plated surface on a substrate that has macroscopic irregularities.

The immediate effect of adding a strong ligand such as cyanide to a plating bath will be to alter the concentration of free metal ion. If we consider

$$M^{n+} + m\text{CN}^- \rightleftharpoons [M(\text{CN})_m]^{(m-n)-} \quad (10)$$

The activity of the free metal ions $a_{M^{n+}}$ is given by

$$a_{M^{n+}} = a_{complex}/K_{stab}(a_{CN})^m \quad (11)$$

where K_{stab} is the stability constant of the cyano complex. Substituting in equation (5) gives

$$E = E^\circ - RT/nF \ln K_{stab} + RT/nF \ln a_{complex}/(a_{CN})^m \quad (12)$$

Since for stable cyano complexes K_{stab} will be large, the $\ln K_{stab}$ term becomes dominant and causes a large negative shift in potential.

This can have some interesting effects. For example, in a mixed copper–zinc bath containing cyanide, since $K_{stab}(\text{Cu}) > K_{stab}(\text{Zn})$, it is possible for the two metals to be deposited at almost the same potential and, indeed, the alloy brass may be plated from such solutions (*vide infra*).

Although metallurgists have done much work on the morphology of the electrodeposited metal and the chemistry of the bulk bath solution can be understood, ideas covering the actual deposition act remain qualitative for the most part. If deposition occurs from an aquo ion, one view[2] of the process is that the ion becomes polarized in a diffusion layer adjacent to the Helmholtz double layer, the water ligands being repelled from the side of the complex approaching the electrode. Removal of coordinated water and discharging then occur in the double layer and the neutral atom is adsorbed on to the electrode surface. Migration of the atom over the surface to a crystal growth point then occurs.

Although there is support for the contention that the discharged metal may move to a site of crystal growth, the prior concept of an uncharged metal atom transferring from the Helmholtz layer to the electrode surface seems less attractive.

A large number of commercially important plating processes occur from complex ion baths in which the metal is a constituent of an anionic complex, *e.g.* copper, zinc, cadmium, silver and gold are all commonly plated from cyanide baths, and tin plates from a stannate bath in which $[\text{Sn}^{\text{IV}}(\text{OH})_6]^{2-}$ is present. Chromium is commonly plated from a chromate bath although in this case the background medium is acid rather than alkaline. Thus the mechanism of deposition of metals from anionic complexes is of particular interest. It will be instructive to comment on two situations, one occurring in alkaline baths, the other in acidic baths.

Although, as explained above, zinc is commonly deposited from cyano baths, it may also be deposited from strongly alkaline baths ('alkaline non-cyanide bath'). Typically a zinc : hydroxide ratio of 1 : 10 would be employed and the major solution species would be the tetrahedral zincate anion $[Zn(OH)_4]^{2-}$ as evidenced from Raman studies.[5] Careful studies have been carried out to investigate the electrode reaction.[6] An electrokinetic study gave data consistent with a four-step mechanism for the overall process

$$[Zn(OH)_4]^{2-} + 2e^- = Zn + 4OH^- \quad (13)$$

The rate determining step was identified as equation (15).

$$[Zn(OH)_4]^{2-} \rightleftharpoons [Zn(OH)_3]^- + OH^- \quad (14)$$

$$[Zn(OH)_3]^- + e^- = [Zn(OH)_2]^- + OH^- \quad (15)$$

There was reason to believe that the dissociation step in equation (14) was in fact a proton transfer

$$[Zn(OH)_4]^{2-} + HOH \rightleftharpoons [(HO)_3Zn(H_2O)]^- + OH^- \quad (16)$$

and that, therefore, the complex species present may be written as $[Zn(OH)_i(H_2O)_{4-i}]^{2-i}$. A range of possibilities exists for the step following the rate determining step. Since mechanisms requiring the adsorption of negatively charged species on an electrode at a high negative potential may be rejected as unlikely, choice fell upon a mechanism requiring deposition of zinc from an uncharged species, the data favouring the following overall process

$$\left.\begin{aligned} [Zn(OH)_4]^{2-} &\rightleftharpoons [Zn(OH)_3]^- + OH^- \\ [Zn(OH)_3]^- + e^- &\longrightarrow [Zn(OH)_2]^- + OH^- \\ [Zn(OH)_2]^- &\rightleftharpoons [Zn(OH)] + OH^- \\ [Zn(OH)] + e^- &\longrightarrow Zn + OH^- \end{aligned}\right\} \quad (17)$$

The rate determining step need not always be, as in this case, one of the reduction steps. Thus at low overpotential, slow surface diffusion was rate determining for the deposition of copper.[7]

Plating from chromate(VI) baths involves an altogether more complex set of processes which are not yet fully understood.[8] The dominant ions in the baths are $[HCrO_4]^-$ when the solutions are dilute, and $[HCr_2O_7]^-$ when more concentrated. A quantity of chromium(III) is generally present. In the absence of foreign ions a film forms on the cathode ('basic chromium chromate') which, whilst porous to hydrogen, prevents reduction of the chromate(VI) species. The presence of foreign anions, particularly fluoride or sulfate, will loosen the film and allow reduction of chromate to proceed. Complexes of sulfate with chromium(III) have been incriminated. It is believed that their solubility can prevent the formation of the film and can help to break down the film initially formed. Certainly one complex containing $Cr:SO_4 = 2:1$ has been identified. This stoichiometry suggests a bridging sulfato complex.

It has been established that most cathode metals are to some extent soluble in chromic acid solutions, and ions will enter the solution in the highest available oxidation state [*e.g.* copper(II), gold(III)]. Polarization of the cathode will then cause reduction to lower oxidation states [kinetic factors will prevent the prior reduction of chromate(VI)], then new low-valent species may then initiate a chemical reduction of the chromium(VI). Chromium deposition occurs within the potential range for the evolution of dihydrogen and, indeed, the latter is the dominant cathode process with the result that typically cathode current efficiencies of only 10–20% are achieved (see equation 9).

Although some chromium(III) is initially present in the bath, early radiochemical data[10] suggest that the deposited chromium does originate exclusively from chromate(VI).

57.2.4 Addition Reagents

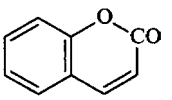
The success of a commercial process depends very much on addition reagents. Two important classes are the levelling agents and the brightening agents.

Levelling agents will encourage deposits to grow more rapidly on microindentations on the surface and less rapidly on peaks, thus achieving a finished surface with a high degree of smoothness. Marketability of a product is usually increased if the electrodeposit is bright. Brighteners can achieve lustrous coatings without the need for subsequent buffing. It is interesting that even coatings of zinc or cadmium, which are unlikely to retain their brightness in use are, none the less, more acceptable to customers when bright.

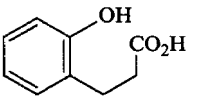
The role, if any, of coordination chemistry in the processes is obscure. Some of the additives are potential ligands, although they may not be effective as such in the bulk solution; however if, as seems likely, they are active at the electrode–solution interface,[11] some possibility of coordination compound formation must be allowed. Examination of deposits has revealed that material which could only have originated from the addition reagent has been incorporated into the electrodeposit.[11] This lends support to the view that the agents do indeed adsorb on to the electrode surface.

It will be neither profitable nor relevant to study each additive to each plating process, but it should be recognized that the additives themselves need not be chemically or electrochemically inert. Some examples follow.

Coumarin (**1**) is a leveller and partial brightener in nickel plating.[11] It can be electrochemically reduced to (**2**): at pH 4, 90% is reduced to (**2**) and only 10% incorporated in the deposit; at pH 2 the figures are 99% and 1%. Melilotic acid (**2**) is poorly adsorbed at the electrode.

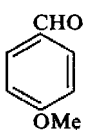


(**1**)

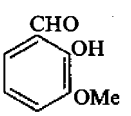


(**2**)

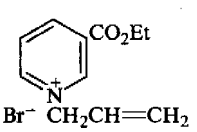
Some recent work on brighteners in zinc plating is also of interest. The first report of successful plating from an alkaline cyanide zinc bath was in 1907[12] but it was not until 1935 that the first bright alkaline cyanide zinc baths appeared in the plating industry. Numerous patents have been issued since 1935 claiming novel brighteners and many commercial processes use mixtures of additives which may act synergistically. A vast range of substances has been employed including metal ions (*e.g.* Ni^{II}, Cr^{III} (but not Cr^{IV}), Se^{IV},Te^{IV}); animal proteins such as glue and gelatine, and aromatic aldehydes such as *p*-anisaldehyde (**3**) or *o*-vanillin (**4**) have more recently proved effective. An important patent[13] introduced a new family of brighteners of which compounds (**5**)–(**8**) are examples. The compounds are effective for alkaline non-cyanide baths as well as for the cyanide baths. Another patent[14] added a range of aromatic betaines to the list of effective compounds.



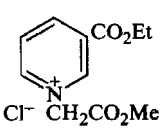
(**3**)



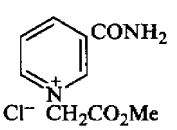
(**4**)



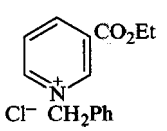
(**5**)



(**6**)



(**7**)

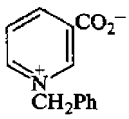


(**8**)

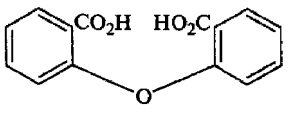
Probably the most widely used compound is 1-benzylpyridinium-3-carboxylate (**9**). It is noted that baths containing this material require a 'working in' period before deposits reach maximum brightness. This correlates with the fact that a new absorption maximum at 360 nm grows when (**9**) is added to alkali. The rate of growth of the maximum is independent of zinc concentration and the rate law is[15]

$$\text{rate} = K_{obs}[OH^-]^2\,[(9)]^2 \qquad (18)$$

Change of the quaternizing group may lead to a slower rate of growth of the 360 nm maximum, and also in practice to a poorer performance as a brightener. Thus it is clear that (**9**) is the precursor of the true brightening agent. There is good evidence to suggest that the mechanism shown in equations (19) and (20) is operative. Whereas (**9**) was unlikely to be an effective ligand for zinc(II) in the plating medium, the so-called bimolecular ether (**11**) is in fact a potential terdentate ligand (*N,N,O* or *O,O,O*). Compound (**11**) is difficult to isolate from solution in a pure form but model compounds (*O,O,O*) or (*O,S,O*) such as (**12**) and (**13**) have been shown to function as ligands to zinc(II) and other transition metal ions.[16] However, complexes of (**12**) and (**13**), which in the solid state are $Zn(L-2H)\cdot 1.5H_2O$ and $Zn(L'-H)(ClO_4)$ (L = **12** and L′ = **13**), decompose on contact with strong alkali. Thus it is improbable that a significant quantity of brightening agent is complexed in the bulk solution (see also Section 57.3.2.6(ii)).



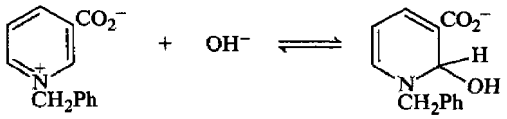
(9)



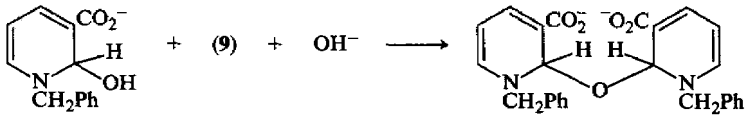
(12)

$HO_2C(CH_2)_2E(CH_2)_2CO_2H$

(13) E = O, S

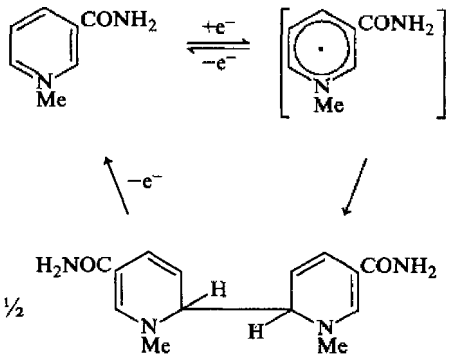


(9) (10) (19)



(11) (20)

The brightening agents may also undergo electrochemical reaction as well as chemical reaction. Thus compounds related to (7) may be electrochemically reduced as shown in equation (21). Thus, dihydropyridine species such as (14) may also be present in the plating bath.



(14) (21)

In view of the fact that species such as (11) and (14) will in any event be derived from (9), it was interesting to note a patent claim[14] for (11) as a new brightener for zinc plating. The claim is doubtless correct, but it is superfluous.

The above examples, which relate to but few of the many possible addition reagents in use, indicate that chemically the systems may be quite complex. The additives are certainly active at the electrode–solution interface and indeed many that are used effectively are known to be surface active. The role of coordination chemistry in the detailed mechanism of action remains somewhat obscure, not so much because the appropriate questions have not been answered, but rather because they have rarely been posed.

57.2.5 Electrodeposition of Specific Metals

It is not relevant within the context of this chapter to detail the technical aspects of the electrodeposition of all possible metals and alloys. Such information is available in a number of specialist texts[1,2] or handbooks.[19] However, it is pertinent to illustrate more specifically than in the above sections the role of coordination compounds in particular cases.

57.2.5.1 Chromium

The point of major interest is that for the most part chromium plating occurs from a chromium(VI) bath (Section 57.2.3).[20] This bath has a low current efficiency, gives off both hydrogen (cathode) and oxygen (anode) and this vigorous evolution of gas causes a mist which creates a health hazard requiring appropriate precautions. Generally a lead anode is used since this is insoluble in the acid medium and will allow the anodic oxidation of chromium(III) to chromate(VI). This obviously requires that the chromium must be replenished as CrO_3. The mechanism of chromium plating has been touched upon earlier (Section 57.2.3) and the role of chromium(III) sulfato complexes was mentioned. Interestingly, in addition to the disadvantageous

role of chromium(III) in creating a cathode film, the presence of some chromium(III) is required to give the bath an adequate throwing power.

The previous remarks can be expanded to include three developments which are designed to overcome some of the unattractive features of the process.

(i) Tetrachromate baths

It is known that trichromates $[Cr_3O_{10}]^{2-}$ and tetrachromates $[Cr_4O_{13}]^{2-}$ may crystallize from strongly acid solutions as their alkali metal salts. Tetrachromates are believed to be major constituents of a plating bath for which the following composition is typical:

CrO_3	300 g l^{-1}	H_2SO_4	0.75 g l^{-1}
NaOH	60 g l^{-1}	Ethanol	1 cm^3 l^{-1}

This 'tetrachromate' bath is characterized by a low operating temperature of 16–22 °C and by an excellent throwing power. Although a high current density requires the bath be cooled, the current efficiency (30–37%) is high by chromium plating standards. The deposit tends to be matt and softish and hence polishing is required for a bright plate and the process will not be suitable if a hard plate is required.

(ii) Trivalent chromium plating

Since the reduction of chromate(VI) to metal is a six-electron process, it would seem logical to plate the metal from an electrolyte based on a lower oxidation state of chromium. A good deal of work has been done on the development of trivalent chromium plating,[8] but it is only recently that a commercial process has been available in the United Kingdom.

The process works with carbon anodes and at a cathode current density of 10 A dm^{-2}. The electrolyte is contained in a plastic or rubber lined bath and air agitation is required. Although a chromium 'complex' is involved, full details of the electrolyte composition are not available in the journal paper reporting the successful development of the new process.[20] Chromium is consumed as the basic sulfate and the ligand is described as inorganic. Conductivity salts are required to improve the conductivity of the solution and some boric acid is present as a buffer.

An earlier American process[21] is equally vague as to details, but chromium(III) chloride complexed with an 'organic' ligand in the presence of a 'secondary organic' (1% v/v) is said to give good results under laboratory conditions. Some chlorine evolution at the graphite anode was observed but one respect in which the process was attractive was that pollution problems seemed generally less severe than with a chromate(VI) bath. One reason is the lower toxicity of chromium(III).

Although the process never translated successfully to industry, more chemical details are available for a system based on aqueous DMF.[22] A typical composition, with quantities in g l^{-1} is:

Cr^{III} (as $CrCl_3 \cdot 6H_2O$)	43	Boric acid	2
NH_4^+ (as NH_4Cl)	10	DMF	400
Na^+ (as NaCl)	20		

The cathode efficiency is 10% (evolution of dihydrogen), 60% ($Cr^{III} \rightarrow Cr^{II}$) and 30% for plating chromium metal. The pH remains constant at 1.4; this is attributed by the authors to the processes shown in equations (22) and (23). However, given an apparent overall mole ratio of Cr:Cl of 1:4.7 and the electrochemical generation of Cr^{II} on which substitution reactions are rapid, it seems that chloro complexes of chromium(III) must be present, in which case equations (22) and(23) may represent an over simplification.

$$2[Cr(H_2O)_6]^{3+} \rightleftharpoons 2[Cr(OH)(H_2O)_5]^{2+} \rightleftharpoons [(H_2O)_4Cr\begin{matrix}O\\ \diagup\ \diagdown\\ O\end{matrix}Cr(H_2O)_4]^{2+} \quad (22)$$

$$2[Cr(H_2O)_6]^{2+} + 2H_3O^+ + [O] \longrightarrow 2[Cr(H_2O)_6]^{3+} + 3H_2O \quad (23)$$

One disadvantage of the chromium(III) process now in operation is that only a limited thickness of plate is possible even at high current density. Indeed, a maximum deposit of just under 0.5 μm is achieved in 3 minutes at 10 A dm^{-2}. Higher current densities actually result in a thinner deposit and only densities in excess of 40 A dm^{-2} restore the thickness achieved at 10 A dm^{-2}. The contrast with the chromate(VI) process is shown in Figure 3.

(iii) Brush plating

Some special instances arise when deposition in an electrodeposition bath would be inappropriate. Small areas can be plated by making a cathodic connection and touching the area with a pad soaked in an electrolyte and in which is located an insoluble anode (often graphite).[8] A popular

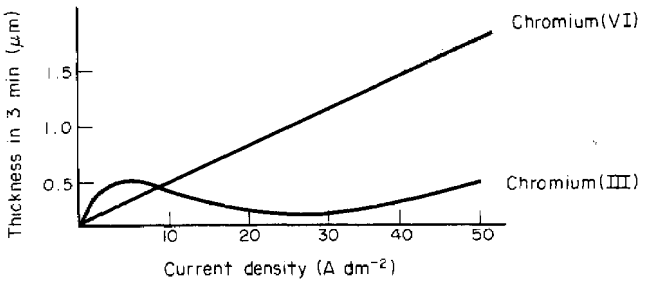


Figure 3 Comparison of thickness of plate deposited in three minutes as a function of current density

choice of electrolyte is the ammonium salt of tris(oxalato)chromate(III), $(NH_4)_3[Cr^{III}(C_2O_4)_3]$, dissolved in methanol or in hydroxylamine.

57.2.5.2 Copper

Three major electrodeposition media for copper may be identified. All involve coordination compounds.

(i) Cyanide copper baths

Cyanide copper baths are of importance for the copper plating of ferrous metals and zinc die castings, often to give protection prior to the deposition of a second metal such as nickel or chromium from a medium (acid) in which the base metal would react. Three baths may be identified: 'Strike', 'Rochelle' and 'High Efficiency'. The Strike bath is valuable for the deposition of thin coatings. The Rochelle bath is robust and generally free from interference by foreign substances and is used for coatings of intermediate thickness. The High Efficiency bath, for which current efficiency can approach 100%, is used for thick coatings but is sensitive to impurities. Typical compositions are given in Table 1.

Table 1 Cyanide Copper Bath Compositions[a]

	Strike ($g\ l^{-1}$)	*Rochelle* ($g\ l^{-1}$)	*High efficiency* ($g\ l^{-1}$)
CuCN	15 (0.168 M)	26 (0.290 M)	75 (0.838 M)
NaCN or KCN	23 (0.469 M)	35 (0.714 M)	93 (1.898 M)
	—	—	115 (1.769 M)
Na_2CO_3	15	30	a
NaOH or KOH	—	—	30
	—	—	42
Rochelle salt $KNaC_4H_4O_6{\cdot}4H_2O$	—	45 (0.160 M)	Optional
Cu:CN	3.79	3.46	3.26 (Na)

[a] These baths contain adventitious carbonate *via* absorption of CO_2 from the air and *via* the anodic oxidative decomposition of cyanide.

Cyanide above that required for a copper:cyanide ratio of 1:3 is termed free cyanide and it is generally assumed that the major cyano complex in solution is $[Cu(CN)_3]^{2-}$. However, this ion was first crystallographically characterized in $Na_2[Cu(CN)_3]{\cdot}3H_2O$ only quite recently.[23] Whilst it is certainly possible that the tricyanocuprate(I) ion is present at lower cyanide concentrations, when a significant excess of the ligand is present it is likely that the tetracyanocuprate(I) is present. However, as seen in Table 1 most baths typically operate with a mole ratio of copper to cyanide between 1:3 and 1:4. The sodium carbonate provides a buffering effect (pH 10.3) in the Strike and Rochelle baths.

The mechanism of deposition is not well understood. The ion $[Cu(CN)_2]^-$ has been implicated but this may be subject to the same objections discussed in Section 57.2.3 when the deposition of zinc was considered. More free cyanide will polarize the cathode with the result that hydrogen

is evolved at the cathode in the Strike and Rochelle baths, although this provides extra cleaning. The free cyanide is also required for the corrosion of the copper anode.

Potassium sodium tartrate (Rochelle salt) is believed to play a complex forming role at both anode and cathode. Thus, the tartrate may complex with the initial products of electrolysis in the anode film and it may also form short-lived complexes in the cathode film.

(ii) Acid copper baths

The history of plating copper from acid baths may be traced back to 1810.[1] The relatively low running costs of the baths make them attractive for electroforming of copper articles and for the electrorefining of copper metal, as well as in standard plating applications. The solutions may be based on copper(II) sulfate/sulfuric acid or, of more recent introduction, copper(II) tetrafluoroborate/fluoroboric acid. The latter solutions may be operated at extremely high current densities and hence are very suitable when heavy deposits are required in a short time; consequently they tend to contain a greater concentration (range 0.94–1.89 M) of copper than do the sulfate baths (range 0.60–1.00 M).

For many applications, addition reagents are required. A bewildering range has been employed for both levelling and brightening; some of the many that are effective include a combination of poly(vinyl alcohol) and glue; amino acids; thiourea; and benzotriazole. As discussed in Section 57.2.4, it is likely that, in many cases, complex formation in the cathode region has some role to play in the mode of action of these reagents. In this context it is interesting that some of the addition agents might be expected to be effective ligands for copper(I). Indeed in one study,[24] a copper(I)–benzotriazole complex was actually identified as an inclusion in the electrodeposit obtained from a benzotriazole-containing copper(II) sulfate acid bath.

(iii) Pyrophosphate copper baths

The advantages of this system are that it presents a much lesser effluent problem than the cyanide bath and, operating around neutral pH, is less corrosive than the acid bath. It has a good throwing power but some metals, *e.g.* steel and zinc, need to be flash plated in a cyanide bath before plating in a pyrophosphate solution is possible.

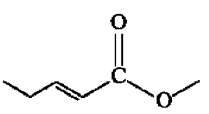
The bath in commercial use is based on potassium bis(pyrophosphato)cuprate(II), which may in fact be isolated as the hexahydrate $K_6[Cu(P_2O_7)_2]\cdot 6H_2O$. Ammonia is generally present, as is a source of nitrate. The ammonia is said to assist in anode corrosion and to contribute to brightening the cathode deposit; nitrate inhibits the reduction of hydrogen ions.

57.2.5.3 Nickel

Nickel is the most widely used electrodeposited metal. It is usually used in connection with chromium when the nickel deposit is followed by one of chromium, the finish being known as 'bright chromium plate'.

The basic bath has altered little since Watts introduced high-speed nickel plating in 1916. The bath is based on nickel(II) sulfate, nickel(II) chloride and boric acid. Whilst this offers little scope for novel coordination chemistry, the importance of nickel plating has ensured that more work than usual has been performed on addition agents[25] and some aspects of this might be profitably considered.

The reduction of coumarin (**1**) mentioned in Section 57.2.4 is typical of the fate of a group of levellers used in nickel plating which have in common the groups (**15**). It has been recognized that the depositing nickel may function as a hydrogenation catalyst and that this would certainly imply adsorption of the alkene on the nickel surface. The vapour phase hydrogenation of ethylene catalyzed by nickel is said to be most rapid when nickel films have the (110) planes preferentially exposed,[26] which may imply that the alkene function shows preferential adsorption on some planes.



(**15**)

The levelling action is also dependent on pH. At lower pH (1.5), greater reduction of (**15**) occurs, *e.g.* to alcohol, and levelling power falls off. At pH 4–5 the alkene function is reduced and a thin film of a hydroxonickel species is seen on the cathode. The leveller and the inorganic film seem to function synergistically to control adsorption of the leveller which, in turn, may influence the development of the nickel surface. Thus again coordination, on this occasion to afford an organometallic species, is implicated but the details of mechanism remain vague and speculative.

Sulfur compounds, *e.g.* arenesulfonic acids, used in conjunction with the unsaturated compounds mentioned above can provide level, bright films. After several hours of operation of the bath, the odour of the aromatic hydrocarbon can be detected and it is well known that the bright deposits contain sulfur. Thus reduction of organic species at the developing nickel surface is a general phenomenon.

57.2.5.4 Precious metals

Those aspects of the plating of silver, gold and the platinum metals which specifically involve coordination compounds are now briefly considered.

(i) Silver and gold

Silver and gold were probably the first metals to be electroplated[27] and were the subject of a patent which could be said to have started the electroplating industry.[28] Both metals are normally plated from cyanide baths and the processes have enjoyed some prominence since World War II as electronics technology has developed and the good electrical conductivity and chemical resistance of the metals has been attractive.

The silver bath normally operates with a mole ratio of Ag:CN between 1:3 and 1:3.27. Potassium carbonate and hydroxide are also present. The excess or 'free' cyanide ensures formation of the dicyanoargenate(I) ion $[Ag(CN)_2]^-$ and prevents precipitation of the sparingly soluble silver(I) cyanide. Generally, a commercial preference exists to add the 'free' cyanide as KCN rather than NaCN.

Many addition reagents have been used to obtain bright silver plate. Most of the successful compounds contain sulfur; indeed, the use of carbon disulfide in 1847 was probably the first recorded instance of an addition reagent improving a deposit.

Chemically the requirements for gold plating are similar. For baths containing a greater concentration of gold the more soluble potassium dicyanoaurate(I), $K[Au(CN)_2]$, is preferred over the sodium salt. The $[Au(CN)_2]^-$ ion is stable over a wide range of pH; below pH 3, however, AuCN precipitates. The pH is normally maintained at less than 11.8 with carbonate and phosphate buffers, which also improve the solution conductivity.

Some baths for flash plating of gold are prepared from solutions of the metal in aqua regia and contain a low concentration of free cyanide. The possibility that tetracyanoaurate(III), $[Au^{III}(CN)_4]^-$, is present in such solutions has been discussed.[29]

(ii) Platinum metals

Only three of the metals, rhodium, palladium and platinum, need be considered. Of these only rhodium plating is of significant commercial importance, but the relatively low cost of palladium has made it attractive for contacts and printed circuits. Electrodeposited platinum is harder than the annealed bulk metal and finds applications in jewellery, the plating of scientific instruments, standard weights and parts of electrical apparatus.

Rhodium is normally plated from a sulfate or phosphate bath. It is palladium and platinum that give more scope for some classic coordination compounds.

Palladium has been successfully plated from baths after introduction as the tetraamminepalladium(II) cation $[Pd(NH_3)_4]^{2+}$, as the nitrite, nitrate or chloride salts. In the latter case, dichlorodiamminepalladium(II) is added to a bath containing ammonium salts (chloride, sulfate and carbonate) and free ammonia. Baths based on $[Pd(NO_2)_4]^{2-}$/NaCl and $[PdCl_4]^{2-}$/NH_4Cl have also been used.

Platinum is generally introduced as dinitrodiammineplatinum(II), $[Pt(NH_3)_2(NO_2)_2]$; the solution also contains ammonium nitrate and sodium nitrite. Alternatively, H_2PtCl_6 or $Na_2[Pt(OH)_6]$, both derivatives of platinum(IV), have been used.

57.2.5.5 Tin

Although relatively soft and expensive, tin has a number of properties such as low toxicity and good resistance to corrosion that make it an attractive plating metal. Since the melting point of the metal is 232 °C, dipping in molten tin is an alternative which has been employed over the centuries, particularly for the tinning of copper cooking utensils. However, little control exists over the thickness of the coating. The formation of steel strip by continuous cold rolling required a process capable of tinning the strip. This is now achieved by electrodepositing tin at speeds as high as 170–600 m min^{-1} using current densities of 20–100 A dm^{-2}.

Two common alternatives are available for electrodepositing tin:[30] alkaline and acidic baths. The alkaline bath has good throwing power but consumes more power than the acid bath. Tin is present in the alkaline bath as stannate(IV), $[Sn(OH)_6]^{2-}$, the bath being approximately 0.25 M in 'free' hydroxide ion (pH 13.4). The hydroxide ion is the principal charge carrier. Potassium is superior to sodium as the counter ion (greater ionic mobility) but economic factors lead to the continued use of sodium in many plants. The hydroxide ions, acting as a sink for dissolved CO_2, also prevent two undesirable reactions (equations 24 and 25).

$$[Sn(OH)_6]^{2-} \rightleftharpoons SnO_2 + 2OH^- + 2H_2O \quad (24)$$

$$[Sn(OH)_6]^{2-} + CO_2 \longrightarrow SnO_2 + CO_3^{2-} + 3H_2O \quad (25)$$

Hydrogen peroxide is present to oxidize any tin(II) to tin(IV). The presence of stannate(II), $[Sn(OH)_3]^-$, causes a spongy non-adherent plate, possibly partly as a result of a disproportionation (equation 26).

$$2[Sn(OH)_3]^- \longrightarrow Sn + [Sn(OH)_6]^{2-} \quad (26)$$

Most interesting is the behaviour of the tin anode. If the anode current density is too low, the tin will dissolve in the alkaline medium as stannate(II) with disastrous results for the plating. If the current density is high, the anode is rendered passive and dioxygen is evolved on electrolysis and the tin must be replenished as stannate(IV). At intermediate current densities of 1–2 A dm^{-2}, the anode assumes a greenish yellow film and the tin enters solution as stannate(IV).

The deposits from the alkaline bath are fine grained, pure, but dull and somewhat porous. If bright non-porous films are required, the plated article is treated in a process known as 'flow brightening' in which it is taken through a bath of palm oil operating at temperatures in excess of 232 °C, the melting point of tin.

The problem of obtaining bright tin deposits direct from the plating bath proved difficult to solve, but it is now possible using acid baths in which organic brightening agents act synergistically with surface active agents. The acid of choice is sulfuric acid (~1.33 M) and the metal is present as tin(II) sulfate (~0.19 M), although the fluoroborates $[HBF_4/Sn(BF_4)_2]$ provide an alternative choice.

Of more interest to coordination chemists is the Du Pont halogen tin process which is based on halo complexes of tin(II). The presence of fluoride is considered to form $[SnF_3]^-$, but much chloride is present to enhance the conductivity. Inhibitors are required to control the oxidation of tin(II) to tin(IV) and the consequent separation of the sparingly soluble $Na_2[SnF_6]$ as a sludge. The process was originally introduced in 1942 for the continuous electrotinning of steel strip.

57.2.5.6 Zinc

Examples in earlier sections have been taken from zinc plating (Sections 57.2.3, 57.2.4); hence it is appropriate that zinc should be the last of the metals selected for individual consideration in this chapter.

Four different processes are available for electrodepositing zinc[31]: (a) high cyanide–high metal (HCHM); (b) low cyanide–low metal (LCLM); (c) alkaline non-cyanide (ANC); and (d) acid (pH 5) (ACID). Typical compositions are given in Table 2.

Table 2 Composition of Zinc Plating Baths (g l^{-1})

	Zinc	*NaCN*	*NaOH*	*Chloride*
HCHM	30–50	75–150	75–150	—
LCLM	7–15	10–30	80–120	—
ANC	12–18	-	115–145	—
ACID	35–55	-	-	140–200

(i) High cyanide–high metal

The electrolyte in these baths is robust and the throwing power of the bath is excellent; however, current efficiency falls with increasing current density as hydrogen evolution increases. The bath also presents significant effluent disposal problems since cyanide must be destroyed by chlorine or hypochlorite oxidation, thus adding to the capital costs of the plant.

The Zn:CN ratio may vary between 1:3.3 and 1:4; however, the Zn:OH ratio is in the range 1:4 to 1:5 and thus the electrolyte will contain both cyano and hydroxo complexes. Indeed, one estimate[32] suggests that as much as 75–90% of the zinc is present as $[Zn(OH)_4]^{2-}$ and the rest as

$[Zn(CN)_4]^{2-}$. It is believed that the mechanism of deposition involves the hydroxo complex,[33] in which case Section 57.2.3 should be consulted.

(ii) Low cyanide–low metal

The main advantage offered by this bath is the reduction of the cost of effluent treatment;[34] however, the low metal content means that stricter day to day analytical control of the bath contents is required. Thus the process is probably viable only if laboratory facilities are available in the same plant. To some extent the disadvantages may be overcome by a compromise move to a medium cyanide–medium metal bath.

The Zn:CN ratio is 1:2, but the Zn:OH ratio is 1:20; hence, the hydroxo- rather than the cyano-zincate will be the major species in the electrolyte.

(iii) Alkaline non-cyanide

A natural development was to remove cyanide altogether from the bath. However, until recently, the bright ductile coatings which were characteristic of the cyanide processes could not be reproduced in the alkaline cyanide-free bath. The development of brighteners such as those discussed in Section 57.2.4 has now made this a viable process which avoids major effluent treatment problems. The current efficiency falls off with current density more rapidly than for the high cyanide–high metal bath, but in this respect it is no worse than the low cyanide bath.

(iv) Acid zinc plating

Acid baths, so called because they operate at a pH of about 5, offer a virtually 100% current efficiency because of the high hydrogen overvoltage; however, until recently they offered poor throwing power and a matt deposit. The development of new brighteners, *e.g.* a mixture of a poly(ethylene glycol) with a ketone[35] or 3-substituted pyridinium compounds,[36] now make this a competitive means of producing decorative zinc plate. Zinc is present in the electrolyte as the aquated cation and chloride is present as a charge carrier.

It is interesting to note[37] an early process which was based on ammonia/ammonium chloride in which the electrolyte contained the tetraammine $[Zn(NH_3)_4]^{2+}$. This solution never found general acceptance, although it has been used for wire plating.

57.2.5.7 Alloy plating

The values of the standard electrode potentials of copper ($Cu^+ + e^- \rightarrow Cu$, 0.522 V) and zinc ($Zn^{2+} + 2e^- \rightarrow Zn$, −0.76 V) make it appear unlikely that the metals could be codeposited as the alloy brass. However, if, for example, solutions which are 0.025 M in $[Zn(CN)_4]^{2-}$ and 0.05 M in $[Cu(CN)_3]^{2-}$ are mixed, simple calculation can show that the static electrode potentials of the two ions have values which approach each other more closely and codeposition becomes much more probable. This can be understood with the help of equation (5) and the knowledge that the dissociation constants of $[Zn(CN)_4]^{2-}$ (1.3×10^{-17}) and $[Cu(CN)_3]^-$ (5.6×10^{-28}) will greatly modify the activity term.

Typical bath constituents for alloy plating are given in Table 3, which also gives some impression of the variety of alloys which may be electrodeposited.

Table 3 Electrodeposition of Alloys: Bath Composition

Alloys	*Bath constituents*	*Alloys*	*Bath constituents*
Ni–Co, Ni–Zn, Ni–Fe	Sulfate, chloride	Ag, Au, Pt alloys	Complex halides
Cu–Zn, Ag–Pb, Ag–Cd,	Cyanide	Cu–Sn	Cyanide, pyrophosphate
Cu–Sn, gold alloys		Ni–Cu	Sulfate, citrate
Pb–Sn, Cd–Sn	BF_4^-	In–Pb	Sulfamate

The use of mixed complex baths is interesting since the concentration of one free metal ion may be altered by varying the amount of one ligand. Thus, in a copper–tin bath, cyanide content may be varied to alter the activity of copper ions, with little or no effect on tin which is present as stannate or as a pyrophosphate complex. It is evident that some knowledge of the coordination chemistry will reduce the degree of empiricism in developing alloy plating baths.

The electrodeposited alloys are alloys in the true metallurgical sense, showing a phase structure indicated by the appropriate phase diagram to be stable at the temperature of electrodeposition; sometimes some interesting differences in behaviour are noted. Thus, for example, cast alloys of

nickel and tin (Ni:Sn = 1:1) contain equal mole fractions of Ni_3Sn_2 and Ni_3Sn_4 whereas the electrodeposited alloy is the single intermetallic compound NiSn.

The NiSn is deposited from a nickel(II) chloride–tin(II) chloride bath containing NH_4HF_2; since the metals are deposited in an accurate 1:1 ratio the involvement of a species such as $NiSnF_4$ has been suggested. It has also been proposed that fluoro-bridged complexes are present and the possibility of trichloro- or trifluoro-stannate(II) complexes has been considered, $X_3Sn \rightarrow Ni^{II}$. A laser Raman study of the solution failed to reveal evidence of species other than aquonickel(II) species and fluorotin(II) species.[38]

57.2.5.8 Miscellaneous ligands

(i) Ammonia

Deposits from solutions of ammine complexes are often good. Two specific examples have been mentioned, namely platinum (Section 57.2.5.4(ii)) and zinc (Section 57.2.5.6). However, such processes have found no large-scale applications.

(ii) Halides

Halides, particularly the less expensive chloride, are often found in plating baths. When a concentrated solution of metal is required, the chloride salt often proves more soluble than the sulfate. The free chloride ions often carry much of the current.

Deposition from true halo complexes can occur; thus good deposits have been reported from $[AuCl_4]^-$ and $[AgI_2]^-$.

(iii) EDTA and related ligands

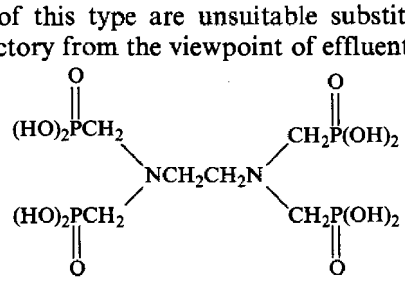
Ethylenediaminetetraacetic acid (EDTA) has found a variety of uses; not all have been successful.

EDTA can be a useful additive to an acid copper bath since it can offer some control over dissolution of the anode. In high-efficiency cyanide copper plating, the addition of EDTA can counter the harmful effects of chromate(VI). It is speculated that the chelating agent facilitates the reduction of Cr^{VI} to Cr^{III} by Cu^{I}.

Iron, which has not been specifically dealt with in this chapter, may be deposited in thin films from alkaline media containing complexes of the metal with EDTA or with triethanolamine.

The effluent disposal problems presented by cyanide baths, together with stricter environmental legislation, have prompted much work to remove cyanide from such systems whilst retaining the good throwing power of cyanide baths and the brightness of the deposits. One approach has been to substitute other ligands for cyanide and EDTA has been a popular choice. Thus, for example, gold will deposit from a gold–EDTA, cyanide-free bath.

A variation of this theme has been the use of related ligands such as ethylenediaminetetraphosphoric acid (**16**).[39] Thus (**16**) and related compounds have been claimed to give satisfactory deposits from cyanide-free, neutral (pH = 7), solutions of copper, nickel, cadmium, iron, cobalt and zinc. Unfortunately, in removing the cyanide problem, ligands of this type create another in that it becomes difficult to free effluent from excess metal. This is well illustrated by a simple example. A solution containing only $[Zn(OH)_4]^{2-}$ is effectively cleared of zinc, as insoluble $Zn(OH)_2$, by adjusting the pH to between 8.5 and 9.0. In the presence of EDTA, no zinc precipitates. Thus chelating agents of this type are unsuitable substitutes for cyanide. By contrast, triethanolamine is very satisfactory from the viewpoint of effluent technology.



(**16**)

57.2.6 Concluding Remarks

The coverage of electrodeposition of metals in this chapter has attempted to identify those aspects of the topic in which coordination compounds have a role. The coverage is not comprehensive in terms of metals that can be electrodeposited, but the examples chosen give a fair

indication of the variety of conditions encountered in terms of pH range, addition reagents and variety of complex species involved. Inevitably, from the viewpoint of the coordination chemist, there is an impression of qualitativeness. In one sense this feeling is understandable since most of the interest in the topic has been metallurgical. After all, commercially speaking, it is the quality and properties of the electrodeposited film that matter rather more than the chemical details of its origin. Some fundamental chemical studies have been carried out but much more work could be done. With a strong resurgence of interest in electrode surface phenomena, more studies of a quantitative nature will doubtless be available in the near future.

57.3 COORDINATION COMPOUNDS AND ELECTRODE PHENOMENA: SURFACE MODIFIED ELECTRODES

57.3.1 Introduction

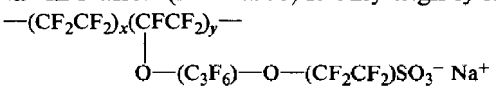
The second topic of this chapter is the role of coordination compounds in advancing electrochemical objectives, particularly in the sphere of chemically modified electrodes. This involves the modification of the surface of a metallic or semiconductor electrode, sometimes by chemical reaction with surface groups and sometimes by adsorption. The attached substrate may be able to ligate, or it may be able to accept by exchange some electroactive species. Possibly some poetic licence will be allowed in defining such species since many interesting data have been obtained with ferrocene derivatives; thus these organometallic compounds will be considered coordination compounds for the purpose of this chapter.

A number of review articles have recently appeared which give a good summary of the present state of progress. No attempt is made to duplicate the coverage of those articles, nor is the coverage given claimed to be comprehensive in the sense that one would expect of a review article; rather an overview of the role of coordination compounds in a topical and exciting area of research is offered. Since most work relates to surface modification, the section is conveniently subdivided into sections dealing with different surface materials. Integrated into these subsections will be details of the various methods by means of which the surface is modified.

57.3.2 Surface Modified Electrodes

57.3.2.1 Nafion modified electrodes

Nafion (**17**) is a perfluorinated polymer related to teflon (polytetrafluoroethylene). An electrode is conveniently coated by allowing an ethanolic solution of the polymer to evaporate. The film produced is stable, rather more so in fact than other polymer films, *e.g.* polyvinylpyridine (see Section 57.3.2.2). At the microscopic level the polymer separates into two phases, the bulk polymer and the lower density ionic cluster phase. Diffusion of ions can occur quite freely; for example, the diffusion coefficient of Na^+ in Nafion (MW 1200) is only slightly less than in water.[44]



(17)

The polymer coated electrode may be doped with an electroactive species by exposing it to a dilute solution of the chosen material. A good example is $[Ru(bipy)_3]^{2+}$ (bipy = 2,2′-bipyridyl), which can be exchanged from a solution of the ruthenium complex in sulfuric acid. It is observed that the value of E° for the $[Ru(bipy)_3]^{2/3+}$ couple is the same as the aqueous solution value. Also the loading of the polymer can be such that the local surface concentration of the electroactive complex is greater than that in the solution from which it is exchanged; thus larger currents are observed than with the bare electrode under the same conditions.

The diffusion of the electroactive ions is both physical and due to electron transfer reactions.[45] The occurrence of either or both mechanisms is a function of the electroactive species present. It has been observed that the detailed electrochemical behaviour of the electroactive species often deviates from the ideal thin film behaviour. For example, for an ideal nernstian reaction under Langmuir isotherm conditions there should be no splitting between the anodic and cathodic peaks in the cyclic voltammogram; further, for a one-electron charge at 25 °C the width at half peak height should be 90.6 mV.[4] In practice a difference between anodic and cathodic potentials may be finite even at slow scan rates. This arises from kinetic effects of phase formation and of interconversion between different forms of the polymer-confined electroactive molecules with different standard potentials.[46]

An interesting example of the type of chemistry that can occur with a Nafion modified electrode is provided by a pyrolytic graphite–Nafion electrode exchanged with $[Ru(bipy)_3]^{2+}$ which is found to catalyze some oxidation reactions. An orange emission is noted at the electrode when the electrolyte is aqueous oxalate at pH 6 (electrogenerated chemiluminescence — ecl).[47,48] Oxalate penetrates the polymer layer and is oxidized by the electrochemically generated $[Ru(bipy)_3]^{3+}$, the following mechanism being proposed (equation 27; L = bipy).

$$\left.\begin{aligned}
RuL_3^{2+} &\longrightarrow RuL_3^{3+} + e^- \\
RuL_3^{3+} + C_2O_4^{2-} &\longrightarrow RuL_3^{2+} + C_2O_4^{\cdot-} \\
C_2O_4^{\cdot-} &\longrightarrow CO_2 + CO_2^{\cdot-} \\
RuL_3^{3+} + CO_2^{\cdot-} &\longrightarrow CO_2 + RuL_3^{*2+} \\
RuL_3^{3+} + CO_2^{\cdot-} &\longrightarrow CO_2 + RuL_3^{2+} \\
RuL_3^{*2+} &\longrightarrow RuL_3^{2+} + h\nu \\
RuL_3^{2+} + CO_2^{\cdot-} &\longrightarrow RuL_3^{+} + CO_2 \\
RuL_3^{+} + RuL_3^{3+} &\longrightarrow RuL_3^{*2+} + RuL_3^{2+}
\end{aligned}\right\} \quad (27)$$

The ecl arises from the reaction of the radical anion $CO_2^{\cdot-}$ with $[Ru(bipy)_3]^{3+}$. It was noted that some quenching of $[Ru(bipy)_3]^{*2+}$ by the ruthenium(III) complex was possible.

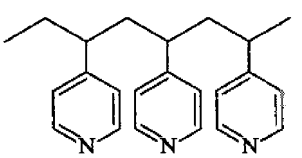
Interestingly, water promotes a non-radiative decay of $[Ru(bipy)_3]^{2+}$. It seems reasonable that within the Nafion film the ruthenium(II) species minimizes its contact with water,[49] which helps to explain the ability of the film to retain relatively hydrophobic counter ions. The more hydrophilic $[Ru(bipy)_3]^{3+}$ is in fact more labile from the film than the bipositive complex.[44]

57.3.2.2 Poly-4-vinylpyridine and related polymers

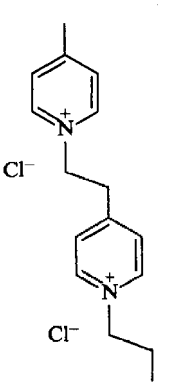
Nafion was rendered electroactive by cation exchange of a redox centre. Other polymers such as poly-4-vinylpyridine (PVP) may be protonated or quaternized to provide the possibility of introducing a redox anion such as $[IrCl_6]^{3-}$ or $[Fe(CN)_6]^{3-}$.[50,51] Alternatively, the pendant pyridyl groups on the neutral polymer may function as ligands and species such as $[Ru(bipy)_2]^{2+}$ may be polymer bound.

(i) Attachment of polymers to electrode surfaces

The polymer may be preformed or, alternatively, the monomer may be polymerized on the electrode surface. In the case of PVP, preformation of the polymer by radical initiated polymerization of 4-vinylpyridine leads to (**18**), but reaction with dry hydrogen chloride gives the ionene form (**19**) which is also an anion exchanger.



(**18**)



(**19**) Ionene polymer

A process commonly used to apply PVP to an electrode surface is to allow a solution of the polymer in a solvent such as methanol to evaporate on the surface. The redox active species can be applied by exposing the modified electrode to a solution of the appropriate complex. Alternatively the PVP–redox complex may be formed prior to coating the electrode. A more sophisticated variation of the above technique is spin casting. A small quantity of polymer solution is dropped on to an electrode, *e.g.* platinum, which is then rotated at thousands of rotations per minute.

Electropolymerization is useful and has been successfully applied to 4-vinylpyridine complexes and to 4-methyl-4′-vinyl-2,2′-bipyridyl.[52] Vinylferrocene (*vide infra*) has been polymerized on to platinum, glassy carbon and titanium dioxide electrodes by introduction to a radiofrequency argon plasma discharge. Electropolymerization and plasma polymerization are likely to be of value to produce copolymers on electrode surfaces.

The techniques described may provide polymer matrices of many monolayers which will generally provide large electrochemical responses since many layers of redox sites can react. The polymer adheres to the electrode surface by adsorption or by covalent, possibly in the case of PVP coordinate, bonding.

Little work has been done with PVP copolymers (that with PVP–lysine is an exception), but it is of interest to note that polymerization with 2% divinylbenzene will produce an insoluble polymer with no impairment of coordinating ability.

(ii) Protonated and quaternized PVP electrode coatings

Protonated or quaternized poly-4-vinylpyridine will function as an anion exchanger; hence ion exchange with anions of interest in redox processes is an easy and obvious way of rendering the polymer redox active. Thus, for example, a graphite disc electrode coated with protonated PVP and exchanged with hexachloroiridate(IV), $[IrCl_6]^{2-}$, has been used to effect the catalytic oxidation of aqueous iron(III).[50] Some leaching of the redox active anions may occur unless the electrode is in contact with a solution containing the same redox species.

The protonated and quaternized PVP will generally swell in contact with solvents, implying ingress of solvent to the polymer matrix. The matrix is a multilayer film, yet redox processes occur with great kinetic facility. This raises the question of how redox centres within the polymer but remote from the electrode–polymer interface can be involved in the necessary oxidation–reduction cycle. One possibility is the migration of the centre through the matrix to the electrode surface. Another possibility is a process of 'electron hopping' between adjacent redox centres. This is illustrated schematically in Figure 4. A centre adjacent to the electrode may be oxidized at an appropriate potential; this will then be reduced by an adjacent centre, and in this way the process will influence chemical events at the polymer/solution interface. In some cases a mixture of diffusion and electron hopping may be involved.[43]

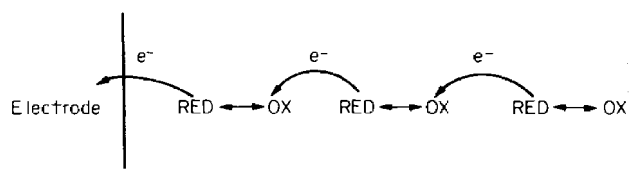


Figure 4 Schematic illustration of 'electron hopping' mode of charge transport in a redox polymer

When an exchanged film is in contact with a solution of the same redox species, the selectivity of the ion exchange medium may render the concentration ratios of reduced to oxidized forms in the polymer film different from corresponding solution values. This may be illustrated by consideration of glassy carbon electrodes covered with films of PVP quaternized with alkyl bromides of varying carbon chain length and exchanged with $[Fe(CN)_6]^{3/4-}$. Accumulation of the iron(III) complex within the polymer matrix is favoured and estimates of the molar work (W^T) for transfer of the the redox ion from the solution to the membrane phase have been made in the presence of potassium trifluoroacetate.[51] The value of W^T_{red} equates to the free energy of dissociation of the ion pair $K^+[Fe(CN)_6]^{4-}$ ($\Delta G = -13$ kJ mol^{-1}). The longer the alkyl chain, the greater the preference for hexacyanoferrate(III), negative values of W^T_{ox} implying ion pair formation, $Q^+{\cdot}[Fe(CN)_6]^{3-}$, within the polymer matrix. For a 12-carbon chain the positive value of W^T_{red} (13 kJ mol^{-1}) implies that total dissociation of the aqueous phase ion pair is required before the iron(II) species can enter the matrix. However, for short carbon chains, which give much better solvated membranes, values of W^T_{red} can become negative, implying that the iron(II) enters these membranes as $K^+[Fe(CN)_6]^{4-}$.

(iii) Redox centres ligated to PVP electrode coatings

Poly-4-vinylpyridine is a versatile polymer since in the non-protonated form it may function as a polymeric nitrogen-donor ligand. Thus, redox centres may be anchored by coordination to pendant 4-pyridyl groups on the polymer chains.

PVP may react with dichlorobis(2,2′-bipyridyl)ruthenium(II) and the precomplexed polymer may then be used to dip coat various electrodes.[52] EDTA complexes of ruthenium(III) will react with PVP and may thereby be immobilized on electrodes. The use of transparent graphite electrodes facilitates the spectroscopic monitoring of both the quantity of PVP and ruthenium on the electrode. Also the $Ru^{III} \rightarrow Ru^{II}$ reduction may be followed as it proceeds. The UV spectra of the immobilized EDTA complexes are similar to those in solution. It has been possible to use a band

at 290 nm to monitor the rate of loss of the Ru^{III}/EDTA complex from the polymer and a rate constant of 4×10^{-4} s^{-1} for the breaking of the 4-pyridyl–ruthenium(III) coordinate bond.[53]

Further variations on the theme have been achieved[54] by anchoring species such as $[Ru^{IV}O(terpy)(py)]^{2+}$ or complexes of osmium.[55] Iron complexes have also been studied; for example, evaporation of a solution containing $[Fe(CN)_5(H_2O)]^{3-}$ and PVP on to an electrode will immobilize the pentacyanoferrate as a pyridyl complex, one in three available pyridyl groups being used to avoid precipitation prior to evaporation of solvent.

The transport of charge by electron hopping is an attractive model for these systems. In the case mentioned above, the electrode response is better from the precomplexed polymer film than from one prepared by first coating with PVP, then dipping into a solution containing a source of $[Fe(CN)_5(H_2O)]^{3-}$; thus the spatial distribution of redox centres is important as well as their number in determining electrode response. Data for the pentacyanoferrate system support charge transport *via* adjacent redox sites and the rate of this transport falls off rapidly below a critical concentration of centres.[56]

The polymer must be able to accommodate geometric changes demanded by the metal ion as the oxidation state changes. Actually, since much work is done with Fe^{II}/Fe^{III}, Ru^{II}/Ru^{III} and Os^{II}/Os^{III}, where in all cases octahedral geometry is dominant, this presents little problem for PVP. Mobility of polymer chains could, however, be an important factor in bringing two redox sites into juxtaposition. Some sophistication is often seen in biological redox polymers where the redox sites are held in favourable spatial relationship and the metal is located in sites which represent a compromise between the geometrical requirements of the oxidized and reduced forms.

The electron transport obeys diffusion laws where studied by transient methods. An experimental system which has provided recent information on conduction in redox polymers consists of a platinum electrode on which the redox polymer is deposited. Porous gold is deposited at the other interface, porous so that charge compensating ions may migrate in and out to the polymer film as the oxidation state of the redox centres changes. In one example the electrode may be represented as $Pt|Os(bipy)_2(PVP)_2^{2+}|Au$. The experiments were then carried out in acetonitrile 0.1 M in $Et_4N^+ClO_4^-$. If the gold electrode is held at 0 V (*vs.* SCE) and the platinum electrode made increasingly positive, the current at each electrode can be monitored as a function of the potential of the platinum electrode. The $E_{1/2}$ for half maximum current was 0.74 V, close to $E^{\circ\prime}$ (0.73 V) for the osmium polymer-bound complex (both figures *vs.* SCE). When the limiting value of current is reached, all sites in contact with the gold electrode are Os^{II} and those contacting the platinum electrode are Os^{III} and steady state concentration gradients exist across the polymer film. Current flows only when mixed oxidation sites are present.[55]

Using the same apparatus it is possible to explore electron mobility involving Os^{II}/Os^{I} and even Os^{I}/Os^{0} (Figure 5). This is achieved by scanning the platinum electrode to negative potential. It was observed that the relative current carrying capacity of the three couples Os^{III}/Os^{II}:Os^{II}/Os^{I}:Os^{I}/Os^{0} was in the ratio 1:3:25, with the most highly conducting state passing currents of 0.6 A cm^{-2}.

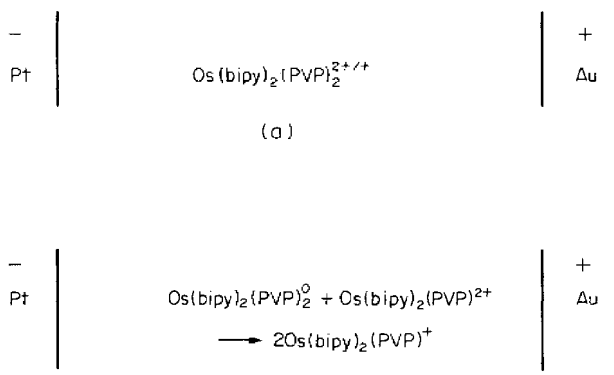


Figure 5 Schematic representation of platinum/porous gold electrode in which the platinum electrode is swept to negative potentials

The electroactivity of a redox polymer may depend upon the solvent with which the surface modified electrode is in contact. Thus, for example, PVP containing an EDTA complex of ruthenium(III) is electroactive in contact with aqueous media, but inactive in contact with solvents such as dimethyl sulfoxide.

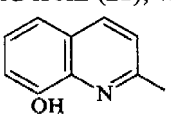
Having debated the mechanism of charge transport within the polymer film, it is now useful to consider a few examples of chemical applications of polymer modified electrodes. Electrodes coated with $[Ru(bipy)_2Cl(PVP)]Cl$ or $[Ru(bipy)_2(py)(PVP)]Cl_2$ show strong catalytic effects for the reduction of cerium(IV) and the oxidation of iron(II).[52]

Another interesting application is the study of the kinetics of thermodynamically unfavourable oxidations of a series of iron, ruthenium and osmium complexes with 2,2′-bipyridyl or 1,10-phenanthroline (ML_3^{2+}) (equation 28). If $E_s^{\circ\prime}$ for $ML_s^{2+/3+}$ is more positive than $E^{\circ\prime}$ for the electrocatalyst, currents will be controlled by the slower rate of equation (28) and k_{12} becomes measurable, thus providing a measure of electron transfer rate in a thermodynamically unfavourable back direction. It was found that the Marcus theory[58] holds in this thermodynamically unfavourable regime. The reaction is driven by the electrode regeneration of Os^{III} in the polymer film. Detailed analysis of kinetic data is consistent with a model in which electron transfer to or from $ML_3^{2+/3+}$ occurs exclusively with the outmost monolayer of the osmium sites on the polymer.

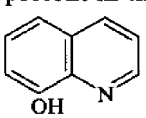
$$Pt|[Os(bipy)_2(PVP)_2]^{3+} + ML_3^{2+} \xrightarrow{k_{12}} Pt|[Os(bipy)_2(PVP)_2]^{2+} + ML_3^{3+} \quad (28)$$
$$-e$$

A number of polymer films related to PVP are known. An obvious variation is polybipyridyl. Thus the complex cation tris(4-vinyl-4′-methyl-2,2′-bipyridyl)ruthenium(II) may be electroreduced in acetonitrile solution to give a polymer film on a platinum electrode. Pulsing of the electrode at 0.5 Hz between +1.5 and −1.5 V (*vs.* SCE) gives an orange emission (ecl) arising from annihilation between Ru^{III} and Ru^{I} centres.[59]

Compounds (**20**) and (**21**) undergo electrochemical oxidation to give films of poly(2-methyl-8-quinolinol) and poly(8-quinolinol) on a variety of metal substrates.[60] Copper(II) can be complexed from aqueous media, but cobalt(II) requires an organic medium. X-ray photoelectron spectroscopy shows the copper(II) complex of films derived from (**20**) to be complexed to both N and O and also shows that water is absent from the primary coordination sphere. However, for cobalt(II) on the polymer derived from (**21**), water is present in the primary coordination shell.



(**20**)



(**21**)

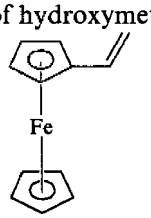
Tetracoordinated copper(II) enhances electron hopping but of the cobalt(II) doped polymers it appears that only those cationic sites adjacent to the metal surface are active.

57.3.2.3 Polyvinylferrocene and related systems

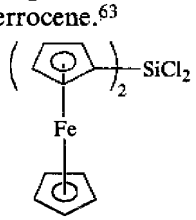
The previous section has illustrated the variety of redox centres that can be used to modify electrode behaviour with the help of polymers containing heterocyclic nitrogen atoms. Thus the redox centre has been retained close to the electrode surface both by ion exchange and by coordination to a pendant group of the polymers. Further variations would be provided either by making the redox centre a pendant group on an appropriate polymer chain, or by seeking some means of binding the atoms covalently to the actual electrode surface. Both possibilities are usefully introduced *via* ferrocene derivatives.

(i) Attachment to the electrode surface

Vinylferrocene (**22**) may be polymerized (Section 57.3.2.2.i) to give a polymer in which the iron(II/III) redox centres are pendant from a carbon backbone. Copolymers have also been formed with styrene[61] and acrylonitrile.[62] Another approach using a different polymer is illustrated by the covalent binding of poly(methacryl chloride) to SnO_2 electrodes followed by attachment of pendant ferrocene centres by reaction of hydroxymethylferrocene.[63]



(**22**)



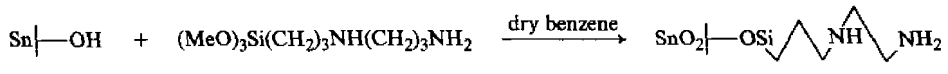
(**23**)

Anodic oxidation of a nickel electrode will give a surface structure that can be represented as Ni—surface—O_xH_y (A). Reaction with, say, a dichlorosilane will then follow (equation 29):

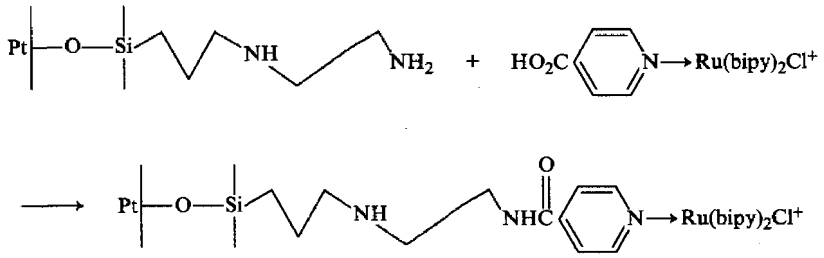
$$(A) + y/2\,Cl_2SiR_2 \longrightarrow Ni\text{—surface—}O_xSiR_2 + yHCl \qquad (29)$$

If (**23**) is selected as the dihalosilane, a convenient way of modifying the nickel surface is available.[64] The electrochemical properties of the treated nickel electrode are very similar to those of a similarly derivatized platinum electrode; for example, both are equally effective in the electrocatalytic oxidation–reduction of solution ferrocene. Normally oxidation of the nickel surface would be a competing process ultimately rendering the electrode passive. The surface modification clearly eliminates this problem and opens up the possibility of using surface modified inexpensive metals as electrodes.

The above example of using silanes to surface modify an electrode is but one of many. The method was pioneered by Murray,[41] who was able to demonstrate the successful reaction depicted in equation (30) by use of X-ray photoelectron spectroscopy. The presence of a good donor group can then be used to coordinate metal based redox centres, or alternatively further organic chemistry may be carried out, *e.g.* following equation (31). The method is then quite general, but is well suited to forming monolayers rather than a multilayer coverage, which characterizes most redox polymer derivatized electrodes.

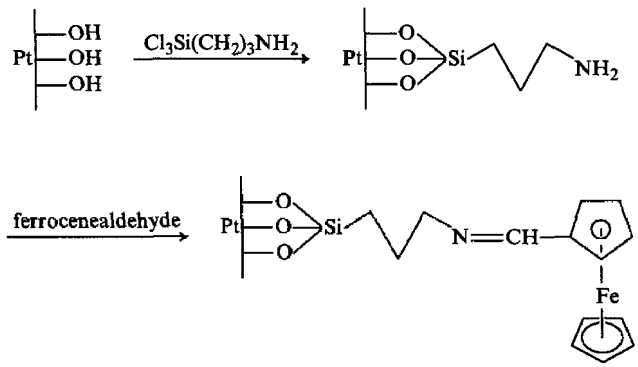


(30)



(31)

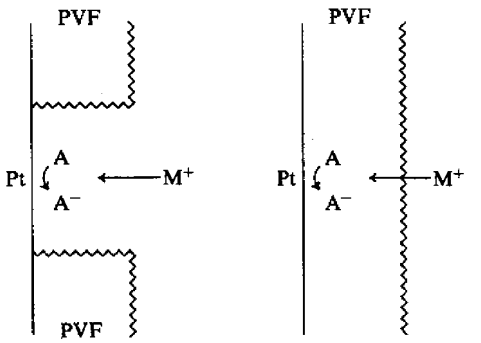
A further example of the use of this technique to introduce a ferrocene redox centre to a platinum surface is given in equation (32). A comparative survey was made of the rates of heterogeneous charge transfer between the platinum electrode and ferrocene both in solution and immobilized on the surface. Both processes show an Arrhenius temperature dependence but $\Delta G_{ACT}(soln) \neq \Delta G_{ACT}(surface\ bound)$. Absolute rate theory was unsatisfactory for the surface reaction and the need to involve electron tunnelling and a specific model for the conformation of the surface was indicated.[66]



(32)

(ii) Some properties of ferrocene modified electrodes

Whilst it is agreed that electron transport within polymer supported ferrocene involves ferrocene–ferrocenium electron hopping and requires no participation from the organic framework, recent studies of electron transfer to a substrate in solution indicate that this need not be mediated by iron(II/III) hopping. Thus X-ray photoelectron spectroscopy gave no evidence for unexposed platinum on an electrode coated with polyvinylferrocene, but scanning electron microscopy revealed channels in the polymer layer. It was concluded that the reactant could either diffuse through such channels or pinholes to the electrode surface, or indeed diffuse through the polymer matrix.[68] These possibilities are illustrated in equation (33).



(33)

Attempts to develop a model for the digital simulation of the cyclic voltammetric behaviour of PVF films on platinum[62] electrodes required inclusion of the following features: (a) environmentally distinct oxidized and reduced sites within the film; (b) interconversion of the above sites and interaction between them; (c) rate of electrochemical reactions to depend on the rate of interconversion of redox sites, the rate of heterogeneous electron transfer between film and substrate, intrafilm electron transfer and the rate of diffusion of counter ions; and (d) dependence on the nature of the supporting electrolyte and the spacing of electroactive groups within the film.

Although the detailed mechanism of electron transport and transfer involving PVF electrodes may be complex, they show remarkable stability and rapidly reversible redox behaviour in non-aqueous solvents such as acetonitrile. This has led to the suggestion[69] that they might function as standard electrodes for non-aqueous solvents. Such standards are required since the SCE is unsatisfactory in a number of respects. Particularly, the liquid junction potential between aqueous and non-aqueous solutions is unknown and irreproducible; also there is a danger that the test solution will become contaminated with water and with potassium and sodium ions.

PVF films may alter the electrochemical response of semiconductor electrodes in useful ways. For example, for potentials more positive than −0.8 V (SCE) only reductions are possible with single crystal or polycrystalline TiO_2 in contact with a ferrocene solution (acetonitrile). However, with plasma coated with PVF, ferrocene sites are oxidized in a potential region where *n*-TiO_2 is considered blocked to electron transfer.[70] Here two factors are involved: obviously the coating of the electrode with an electroactive species, but also alteration of the surface energetics of the semiconductor.

This section can be concluded by reference to an example of a chemical application of a PVF modified electrode.[71] Halocarbons may be electrocatalytically reduced using PVF on carbon as the electrode with photoassistance. The overall scheme is given in equation (34):

$$Fe(Cp)_2 + RX \overset{K}{\rightleftharpoons} Fe(Cp)_2 \cdots XR \xrightarrow[\lambda < 400\,nm]{h\nu} Fe(Cp)_2 + X^- + R^{\cdot} \tag{34}$$

If the electrode is held at the iron(II/III) potential, equation(35) applies.

$$\begin{aligned}
&\text{carbon}\left|Fe(Cp)_2Fe(Cp)_2\right| + RX \overset{K}{\rightleftharpoons} C\left|Fe(Cp)_2Fe(Cp)_2{\cdot}XR\right| \\
&C\left|Fe(Cp)_2Fe(Cp)_2{\cdot}XR\right| \overset{h\nu}{\rightleftharpoons} C\left|Fe(Cp)_2\overset{\delta+}{Fe}(Cp)_2\overset{\delta-}{X}{-}R\right| \\
&C\left|Fe(Cp)_2\overset{\delta+}{Fe}(Cp)_2\overset{\delta-}{X}{-}R\right| \longrightarrow C\left|Fe(Cp)_2\overset{+}{Fe}(Cp)_2\right|\dot{R}{-}X^- \longrightarrow \dot{R} + X^- \\
&\overset{e^-}{\searrow}\ \overset{e^-}{\curvearrowright} \\
&C\left|Fe(Cp)_2\overset{+}{Fe}(Cp)_2\right| \longrightarrow C\left|Fe(Cp)_2Fe(Cp)_2\right|
\end{aligned} \tag{35}$$

57.3.2.4 Prussian Blue modified electrodes

It has already been noted that hexacyanoferrate ions may be exchanged on to protonated and quaternized PVP (Section 57.3.2.2(ii)), and indeed other polymeric ion exchange materials may be used, *e.g.* poly(vinyl sulfate) and poly(styrene sulfonate).[72] Also, similar redox species may be anchored using chlorosilanes, *e.g.* (**24**).[64]

$$Cl_2Si[(CH_2)_3CN]_2\,|\,[Fe^{II}(CN)_5(H_2O)]^{3-}$$

(**24**)

In this section, electrodes with relatively pure films of hexacyanoferrate(II/III) salts will be considered. They can be produced by a variety of means. In one series of experiments, graphite electrodes were treated with $Fe(CO)_5$ in a glow discharge, after which the electrode surface contained iron(III) oxides and carboxylates (from oxidation of carbon monoxide). When the electrode is placed in aqueous $K_4[Fe(CN)_6]$ the $[Fe(CN)_6]^{3/4-}$ couple is attached. The film is stable over many thousand electrochemical cycles and colour changes corresponding to those shown in equation (36) are noted.

$$\underset{\text{Berlin Green}}{[MFe^{III}\{Fe(CN)_6\}]_{0.5}\,[Fe^{III}\{Fe^{III}(CN)_6\}]_{0.5}} \xleftarrow{-\frac{1}{2}e^-,\,-\frac{1}{2}M} \underset{\text{Prussian Blue}}{MFe^{III}[Fe(CN)_6]} \xrightarrow{e^-,\,M} \underset{\text{Everitt's salt}}{[M_2Fe^{II}\{Fe(CN)_6\}]} \quad (36)$$

Films of Prussian Blue may be electrodeposited on materials such as platinum, glassy carbon, SnO_2 or gold. The electrodes are cathodically polarized in solutions of iron(III)/$[Fe^{III}(CN)_6]^{3-}$ which are 0.01 M in HCl. Deposits of Prussian Blue are obtained most rapidly on gold and rather less rapidly on SnO_2. Some ^{57}Fe Mössbauer data have been obtained for films on transparent SnO_2 (which may have some value as electrochromic displays). Thus at 0.6 V the parameters are δ = 0.37 mm s^{-1}, Δ = 0.41 mm s^{-1}; at −0.2 V (SCE), δ = 1.14 mm s^{-1}, Δ = 1.13 mm s^{-1}. These data, together with ESCA measurements, serve to indicate that the film is indeed water insoluble Prussian Blue, $Fe_4[Fe(CN)_6]_3$. The optical spectrum of the electrode was studied as a function of potential with the results given in Table 4. The voltammetric wave at −0.2 V was found to be dependent on the nature of the supporting cation in solution; the cations may therefore migrate into the open 'zeolitic' structure.[74]

Table 4 Optical Maxima of Prussian Blue on SnO_2 as a Function of Potential

Potential of electrode[a] (V)	*Optical maxima* (nm)	*Potential of electrode*[a] (V)	*Optical maxima* (nm)
0.6	700 (Prussian Blue)	1.4	420 (fully oxidized)
−0.2	No distinct visible bands	1.1	420, 770[b]

[a] SCE.
[b] 770 nm band is intervalence charge transfer and varies with the degree of oxidation.

Some further information on the migration of supporting cations through zeolitic channels in the Prussian Blue type of structure comes from a study of a related system, $Cu[Fe(CN)_6]$.[75] The copper(II) hexacyanoferrate(II) may be electrodeposited on glassy carbon when cyclic voltammetry reveals two redox couples at 0.69 V (reversible, Fe) and 0.00 V (cathodic), 0.35 V (anodic) (Cu). Potassium ions are transported into the film during reduction preferentially to sodium. This observation correlates with effective ionic size (K^+, 2.4 Å; Na^+(aq), 3.6 Å) in comparison with the zeolitic channel size (3.2 Å), although it is not in fact possible to return the film to the potassium only form after exposure to aquated sodium ions. However, potassium will displace totally the larger aquated lithium ion (4.7 Å). The results of the study indicated a very low barrier to electron transfer in $Cu[Fe(CN)_6]$ films and, in contrast to the immobilized redox polymer mediations considered earlier, the behaviour of the film is similar to a conductor in that solution species undergo reactions governed by their redox potentials and independently of the film redox reaction.

Deposition of $Cu[Fe(CN)_6]$ on to transparent SnO_2 gives an optically transparent electrode which undergoes a marked change in the visible spectrum on redox reaction, thus making this material a further candidate for electrochromic devices.

The possibility of using surface modification of cheap metals to make them effective electrode materials has been mentioned (Section 57.3.2.3(i)). A further example employs cyanoferrates and cyanoruthenates as the redox centres.[76] Complexes such as $[M(CN)_5L]^{n-}$ (M = Fe, Ru; L = CN, H_2O, NO, L-histidine) may be immobilized on a partially corroded nickel surface. The surfaces have good stability and diffuse reflectance IR spectroscopy shows the presence of bridging cyano groups, implying the presence of a binuclear (Ni, M) species in the surface. A general equation for the redox reaction is:

$$R_x\left[Ni^{II}(NC)\,M^{III}(CN)_5\right]_y \underset{-e^-}{\overset{+e^-}{\rightleftharpoons}} R_z\left[Ni^{II}(NC)\,M^{II}(CN)_5\right]_y \quad (37)$$

The redox potential is found to be a function of the ionic size of R, varying over 500 mV for the series Li–Cs, thus raising the possibility of developing ion sensitive electrodes.

57.3.2.5 Miscellaneous surface modified electrodes

In the foregoing sections, surface modifications by materials which have received significant attention have been gathered under separate headings. In this section, other modifications to electrode surfaces which have involved coordination compounds are considered.

(i) Clay modified electrodes

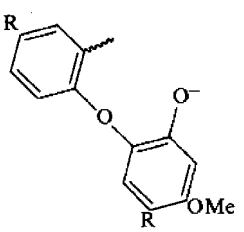
Montmorillonites (smectite clays) have structures resembling that of pyrophyllite but the structure is not electrically neutral. Exchangeable cations are located in interlamellar regions of the clay and, furthermore, the clay can be flocculated such that the plate-like crystals compact with parallel *c*-axes to give coherent layers. The smectites are then attractive materials with which to modify electrodes.

Some experiments have been carried out with a sodium montmorillonite dispersion on an SnO_2 electrode.[77] The layer of clay adhered well to the surface and $[Ru(bipy)_3]^{2+}$ was successfully exchanged on to the clay. The film was electroactive but cracked readily. The addition of powdered platinum gave a more coherent layer. Other species exchanged on to the clay included $[Fe(bipy)_3]^{2+}$ and a trimethylammonium derivatized ferrocene.

An interesting variation is to exchange an optically pure tris chelate complex on to montmorillonite, *e.g.* Δ-$[Ru(phen)_3]^{2+}$. If this clay is used to modify the surface of an SnO_2 electrode, it is found that the electrochemical oxidation of $[Co(phen)_3]^{2+}$ at 30 °C produced Λ-$[Co(phen)_3]^{2+}$ with 7% optical purity.[78]

(ii) Novel polymers

The electrochemical oxidation of tyramine in NaOH/MeOH media gives films of polytyramine (**25**). The film, on a platinum electrode, can complex copper(II) ions from aqueous media and cobalt(II), iron(II), manganese(II) and zinc(II) from organic media. X-ray photoelectron spectroscopy established that coordination of the metal ions had occurred. For cobalt, evidence of coordination to both ether and amine functions is obtained, but for the other metal ions evidence of ether coordination is less definitive.



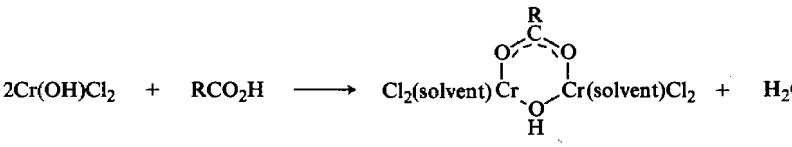
(**25**) $R = CH_2CH_2NH_2$

Cyclic voltammetric studies show a strong pH dependence for the electrode response when doped with copper. Free amino groups protonate at low pH, causing swelling of the polymer and a more open structure. The detailed redox behaviour of the copper electrode is determined by the rate of charge diffusion through the film.

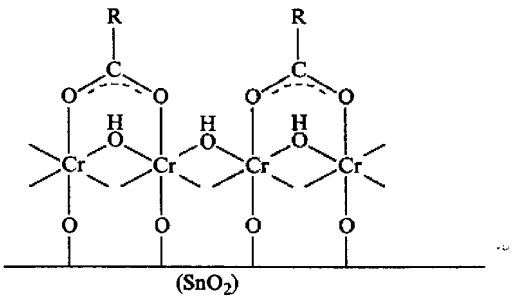
By contrast, the cobalt and iron doped electrodes form a perfectly reversible redox system showing voltammograms which are independent of film thickness. It was suggested that differences arose from more facile electron hopping in the case of 'four coordinate' copper(II) than for five or six coordinate $M^{II/III}$ (M = Co, Fe). Electrodes doped with manganese(II) or zinc(II) gave no response.

Polymeric coatings considered thus far have been based on organic polymers. An example of an electrode (SnO_2 on glass) modified with a coordination polymer is now considered.[79] Complexes of chromium(III) with carboxylic acids have a variety of uses. For example, 'volan', a chromium(III)–methacrylate complex, is used as a coupling agent for reinforced plastic laminates. Stearic acid complexes are used to waterproof paper and cotton. The structure of such complexes appears uncertain but reasonable speculation suggests that equation (38) may be valid. Thus, if a surface containing OH groups (*e.g.* SnO_2) was treated with a pH adjusted solution of the complex, condensation polymerization of the complex can occur (**26**). If R is chosen as ferrocenyl, cyclic voltammograms in acetonitrile ($NBu_4^+ClO_4^-$) are the same as those for surface attached ferrocene (Section 57.3.2.3).

A novel approach to electrode design using polymeric ligands was recently illustrated using the nickel–triphenylphosphine system.[80] An effective homogeneous electroactive catalyst (Ni/PPh_3) is solubilized with 2% crosslinked polystyrene phenylphosphine. The complexed polymer is then

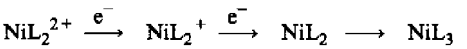


(38)



(26)

mixed with graphite paste to form a 'physical mixture' electrode which, it is claimed, has a longer life than a surface modified electrode and is effective in electrocatalysis without the need for coordinating ligands in solution. Charge is readily transferred in and out of the electrode and the cathodic electrochemistry is similar to the solution electrochemistry, *e.g.* equation (39).

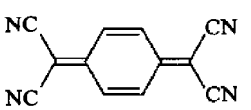


(39)

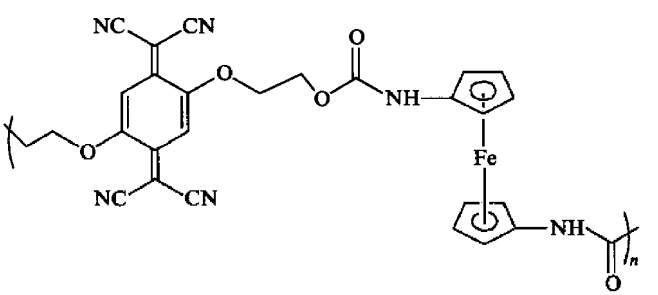
L = phosphine; NiL_3 is most stable for Ni^0

(The bis-phosphine complex must live long enough to capture a further phosphine ligand or else nickel metal precipitates.) It is predicted that other metals should be effective in such physical mixtures, in which case the idea has greater potential.

Much work has been undertaken to modify electrode surfaces with films which are themselves conducting. The most promising approaches involve organic charge transfer and radical ion polymers. Coordination chemistry has, to date, played little part in this work (a good recent review is available),[67] but one example relating to ferrocene chemistry can be quoted. In this example a well known electron acceptor, 7,7′,8,8′-tetracyanoquinodimethane (TCNQ; **27**), is modified and incorporated into polymer (**28**) in which the iron(II) of the ferrocene unit is the electron donor. The electrical conductivity of such a film will depend on partial electron transfer between ion and TCNQ centres as well as on the stacking of the polymer chains. The chemistry of other materials, based on coordination compounds, which have enhanced electrical conductivity is covered in Chapter 61.



(27) TCNQ



(28)

(iii) Phthalocyanine

Dye molecules covalently attached or adsorbed on to semiconductor electrodes may sensitize the electrode to visible light. Thus it may be possible to produce photocurrents and photovoltages corresponding to longer wavelengths of light than would correlate with the semiconductor band gap.

Metal phthalocyanines (MPc) are a very attractive choice of dye since they are stable and the chromophores absorb strongly in the solar spectrum. Also a wide variety of metal phthalocyanines are known; thus a wide range of redox potentials is available, and indeed some are semiconductors in their own right.

The semiconductors *n*-TiO_2 and *n*-WO_3 have been sensitized with thin films (100–250 Å) of MPc (M = Mg, Zn, TiO, Co, Fe, ClAl, H_2)[81] and have been shown to effect the photo-oxidation of I^-, $[Fe(CN)_6]^{4-}$, hydroquinone and $[Fe^{II}(EDTA)]^{2-}$. Photocurrents were proportional to the light

intensity and the spectral response was characteristic of the MPc film. If the electrode was held at negative potentials, the photosensitized reduction of benzoquinone, $[Fe^{III}(EDTA)]^-$ and dioxygen occurred. This is consistent with *p*-type semiconductor behaviour of the MPc films.

Iron phthalocyanine derivatives are amongst the most powerful catalysts for dioxygen reduction, but thin films of FePc on glassy carbon show deactivation on repeated electrochemical cycling.[82] The cyclic voltammogram of FePc (3000 Å) on gold in helium-saturated 0.5 M H_2SO_4 shows three anodic and three cathodic waves, each corresponding to a one-electron change. It was concluded that the waves corresponded to dihydrogen adsorption and desorption at different surface sites.

The electrode will promote the reduction of dioxygen, the reduction wave shifting from −0.5 V on bare gold to −0.05 V on the FePc film, but the intensity of the wave decays on repeated scanning indicating some deactivation process. The deactivation is caused by a combination of blocking by peroxide intermediates and actual loss of iron centres from the film.

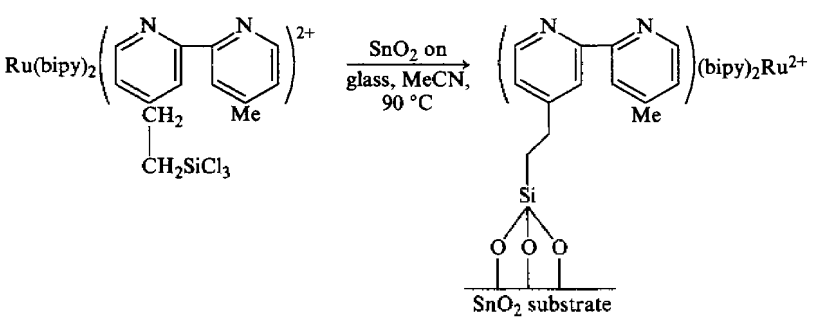
(iv) Bipyridyl, phenanthroline and related systems

Complex cations containing 2,2′-bipyridyl or 1,10-phenanthroline as ligands, particularly those of ruthenium, have been encountered in Section 57.3.2.2(iii). However, the bis-chelate complex was generally anchored to a polymer chain by coordination to pendant pyridyl groups although the possibility of electrochemical polymerization of a 4-vinyl-4-methyl-2,2′-bipyridyl was considered.[59] In this section, some miscellaneous examples of the role of bipyridyl and phenanthroline complexes are considered.

The theme of photosensitizing semiconductor electrodes introduced in Section 57.3.2.5(iii) may be developed with an example from ruthenium–bipyridyl chemistry. The sequence (40) is well known. The effectiveness of the photosensitization should be increased by the covalent attachment of the tris(bipyridyl)ruthenium(II) entity to the semiconductor surface, for example to SnO_2. This has been achieved using the versatile halosilane chemistry shown in equation (41). The counter anion was PF_6^-. Cyclic voltammetry showed that the behaviour of the systems SnO_2/aqueous $[Ru(bipy)_3]^{2+}$ and SnO_2(film)/electrolyte were very similar but with a +0.05 V shift in E°. The coated electrode gives a photocurrent with a red shift of 10 nm which is twice as large as for the non-coated electrode. Unfortunately the current falls off due to promotion of the hydrolysis of the film.

$$[Ru(bipy)_3]^{2+} \xrightarrow{h\nu} [Ru(bipy)_3^*]^{2+} \xrightarrow{+e^-} [Ru(bipy)_3]^{+}\ (RED) \qquad (40)$$

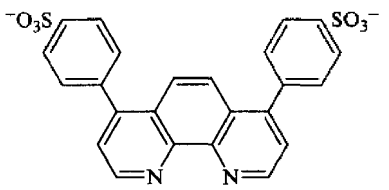
$$[Ru(bipy)_3^*]^{2+} \xrightarrow[(\varepsilon = 1.4 \times 10^4\ M^{-1}\ cm^{-1})]{\lambda = 455\ nm} [Ru(bipy)_3]^{3+}\ (OX) \xrightarrow{-e^-} [Ru(bipy)_3^*]^{2+}$$



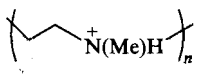
(41)

A neat exploitation of the ideas of Section 57.3.2.2(ii) is achieved *via* the ligand bathophenanthrolinedisulfonic acid (**29**), which can be ion exchanged on to a quaternized polymer such as poly(*N*-methylethylenimine) (**30**). Subsequent treatment with iron(II) will give the orange-red bathophenanthroline complex.[84] An interesting potential application as an electrochromic device is illustrated by sputtering Al_2O_3 on to an SnO_2 surface, except for seven segments defining the number '8' as in a digital display. Treatment of the surface with the bathophenanthroline polymer gives an orange-red colour. If the potential of the electrode is held at +1.2 V (*vs.* SCE; $Fe^{II} \rightarrow Fe^{III}$), within 0.2 s a negative '8' appears.

Bis(1,10-phenanthroline)copper(I) has an absorption spectrum which is a function of concentration. This has been attributed to oligomerization, possibly *via* π–π intermolecular stacking interactions. The tendency to oligomerize has a marked effect on the electrochemistry of the complex. For example, the complex exhibits extensive adsorption on the surface of a graphite electrode. The multilayers exhibit good electron mobility and the layers probably grow by reduction of surface copper(II). Rotating disc voltammetric measurements of the reduction of



(29)



(30)

$[Cu^{II}(phen)_2]^{2+}$ on electrodes coated with $[Cu^{I}(phen)_2]^{+}$ allowed estimation of the rate constant for electron transfer between the two complexes, a value of 10^5 M^{-1} s^{-1} being obtained.[85]

1,10-Phenanthroline inhibits the anodic dissolution of iron and the new technique of surface-enhanced Raman spectroscopy (SERS) has identified the presence of $[Fe(phen)_3]^{2+}$ on the electrode surface during dissolution.

4,4′-Bipyridyl has been used to modify silver electrodes to overcome the sluggish response of proteins at the electrodes. Strong SERS is observed both at the oxidation (+0.45 V) and reduction (−0.6 V) potentials, indicating that the ligand remains adsorbed. The spectra observed as a function of potential show the presence of Ag^{I}–bipy complexes, silver metal with adsorbed bipyridyl and, at −1.4 V, bipy → $bipy^{-}$.[87]

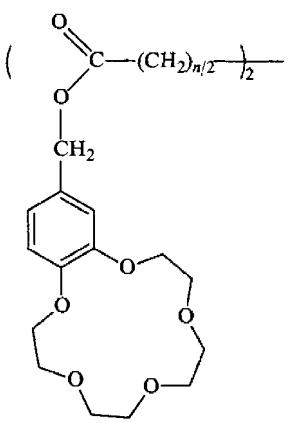
57.3.2.6 Applications

In this section, many of the objectives driving current research in the field of modified electrode surfaces are identified. The constraint that the application should involve coordination compounds is applied; hence a somewhat constricted view is obtained which is nonetheless, fortuitously, reasonably comprehensive.

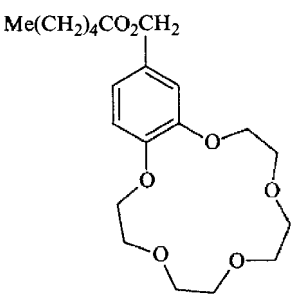
(i) Ion selective electrodes

The development of electrodes to measure rapidly the concentration of ions to which they are uniquely sensitive has important applications in many fields. Two recent examples are quoted of surface modification of an electrode with a ligand showing some specificity for particular ions.

In one approach crown ethers (**31**) or (**32**) are mixed with PVC and a plasticizer such as *o*-nitrophenyl octyl ether in THF to give a membrane on evaporation of the solvent. Discs may then be cut and incorporated into electrodes. The resulting electrodes show good selectivity for thallium(I) and are useful in the measurement of thallium concentrations.[88]



(31)

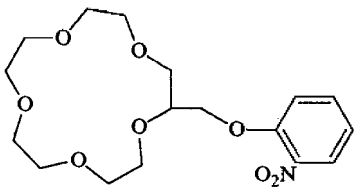


(32)

Enhanced binding of sodium ions by electrochemically reduced nitrobenzene substituted lariat ethers (*e.g.* **33**) has been observed.[89] This is attributed to interaction between ring bound Na^{+} and the reduced side chain. Log K_s (**33**·Na) has been estimated to be 6.33, where K_s is the binding constant for Na^{+} and the anion of (**33**).

(ii) Reactions at electrodes

Nafion modified electrodes (Section 57.3.2.1) have been shown to promote electrogenerated chemiluminescence from the $[Ru(bipy)_3]^{2+}$/oxalate system.[44] The problem of the quenching of the ecl by water was overcome in the Nafion case since sections of the electrode coating were hydrophobic. However, aqueous systems continue to be of interest in the development of practical ecl devices such as digital display units (see also Section 57.3.2.5(iv)). It has been shown that ecl is



(33)

obtained at the surface of a platinum or glassy carbon electrode immersed in an aqueous solution which is 10^{-3} M in $[Ru(bipy)_3]^{2+}$ and 5×10^{-3} M in oxalate when a potential more positive than that required for oxidation of the ruthenium(II) complex is applied. The pH should be $\geqslant 2$. Removal of dioxygen is not necessary, but the intensity of the orange luminescence is enhanced by flushing with dinitrogen. Other organic acids such as pyremic, malonic and lactic acids are effective.[90]

A different application of ecl is illustrated by the alternating current electrolysis of transition metal carbonyl complexes. Figure 6 shows the cycling of a complex A between oxidized and reduced forms. Use of alternating current electrolysis enables chemical use to be made of ecl. For example, reaction (42) is known to be achievable by conventional photochemical means and can also be carried out by applying an alternating potential in an electrochemical cell.[91]

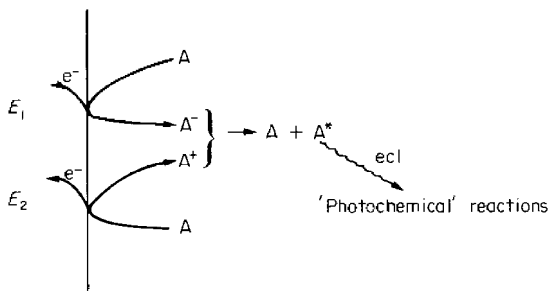
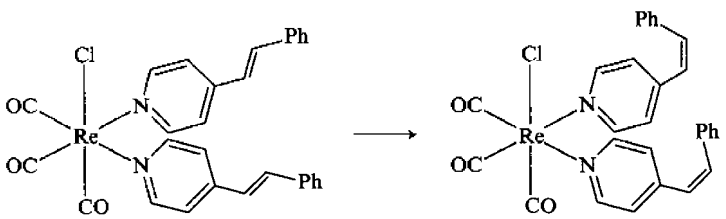


Figure 6 Cycling between E_1 (RED) and E_2 (OX) to produce ecl

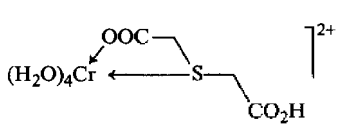


(42)

The phenomenon of ligand bridging between redox centres in homogeneous electron transfer reactions is well established. It has now been shown that such ligands may adsorb on to the electrode surface and mediate electron transfer to or from the electrode from some oxidizable or reducible species in solution.

Sulfur atoms in thiolate or thioether ligands are well known for their ability to mediate electron transfer in homogeneous redox reactions; indeed, in reactions involving chromium(II), a Cr^{III}—S bond is often found in the product, indicating an inner sphere mechanism.

If chromium(II) is oxidized at a mercury electrode in the presence of $S(CH_2CO_2H)_2$, there is extensive incorporation of the thioether in the chromium(II) product when the oxidation is carried out between −0.3 and −0.4 V (*vs.* SCE), but incorporation diminishes at more positive potentials. It is argued that the initial chromium(III) product may be (**34**) in which the chromium–sulfur bond is labile.[92]



(**34**) $K_{formation} \approx 4 \times 10^{-4}$

The thioether (**13**) considered above has previously been mentioned in Section 57.2.4, when it was concluded that substantial complexing of zinc ions in the bulk solution of a plating bath did not occur. This work now establishes that such agents can be active at the electrode surface and helps to establish that adsorption on to the electrode must be an important prelude to the effective action of addition reagents in electroplating.

Both Ru^{III}(EDTA) and Ru^{III}(HEDTA) (HEDTA = *N*-2-hydroxyethylenediaminetriacetato-) are adsorbed at mercury electrodes, but if a ligand is present which can bind the labile sixth coordination position, adsorption is reduced. Thiocyanate is effective in reducing the quantity of complex adsorbed, possibly due to the formation of a thiocyanato complex.[93]

(iii) Electrocatalysis

Equations such as (1) in many cases have a rate constant that has the Arrhenius form even when they occur at the electrode surface (equation 43):

$$k = A \exp(-E_a/RT) \tag{43}$$

(k = rate constant, A = frequency factor, E_a = activation energy). An important difference between a reaction occurring at the electrode surface and that in homogeneous solution is that the rate of the process depends on the potential of the electrode. Since the electrons can be considered reactants, a more negative potential will effectively stabilize the reactants and, hence, lower E_a. It is seen that rate constants for oxidation and reduction processes vary in opposite senses with potential.

Some reactions are kinetically facile. A good example is the reduction of $[Ru(NH_3)_6]^{3+}$ since this involves a one-electron change and no major stereochemical change between oxidized and reduced species. Furthermore, no adsorbed intermediates are involved. Where the reaction is more complex involving several steps and adsorbed intermediates, it is often necessary to apply a more extreme potential than that implied by thermodynamic considerations in order to see an enhancement of the rate constant.

Many electrode reactions are potentially attractive but may be too slow for practical application. An electrocatalyst may increase the rate to practicable values and often takes the form of a modification to the electrode surface.

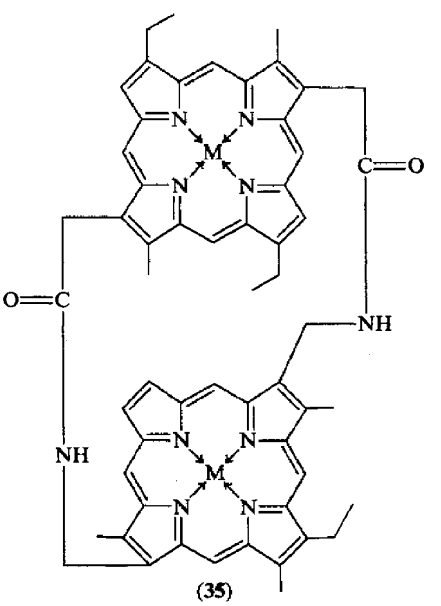
A popular reaction for study has been that shown in equation (44), which is actually a rather complex process which proceeds through high-energy intermediates and has a tendency to stop after the addition of only two electrons (equation 45).

$$O_2 + 4H^+ + 4e^- \longrightarrow 2H_2O \tag{44}$$

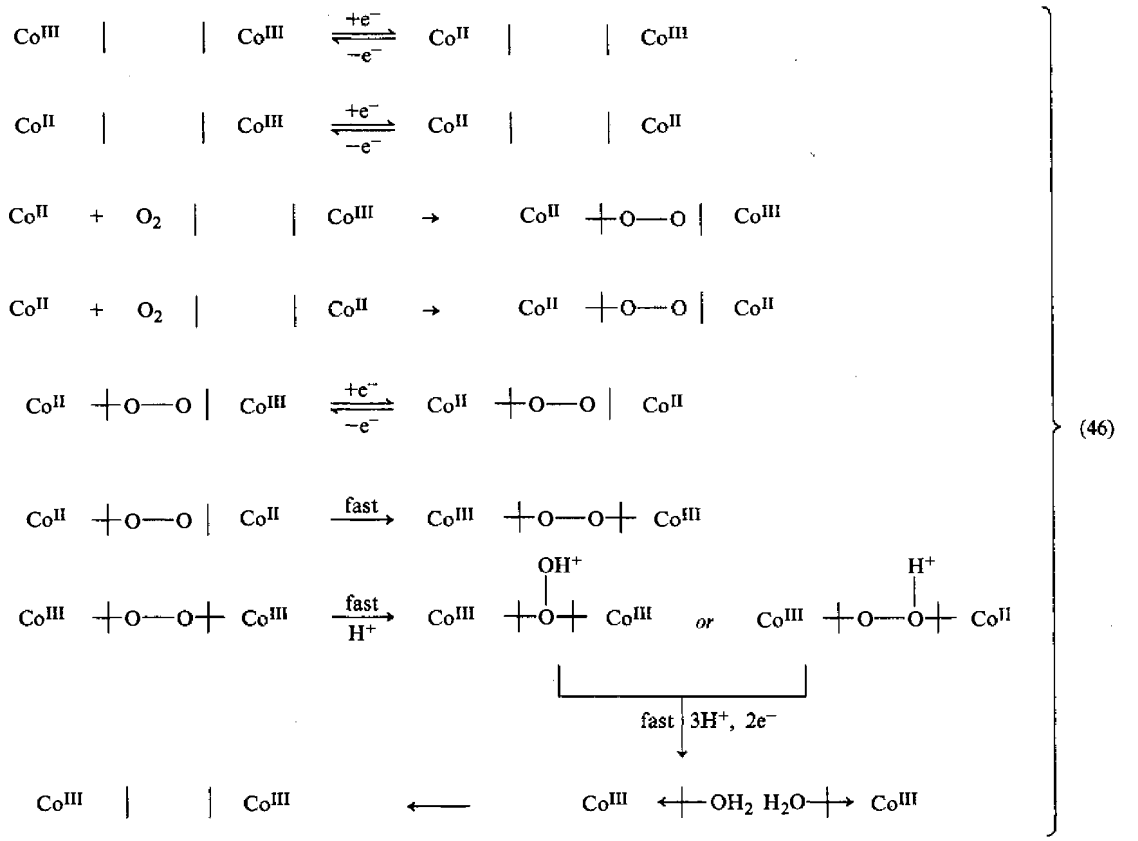
$$O_2 + 2H^+ + 2e^- \longrightarrow H_2O_2 \tag{45}$$

One of the economic incentives for the study of reaction (44) is that the reaction relates to the successful development of methanol–oxygen and hydrogen–oxygen fuel cells which are capable of extremely efficient conversion of the energy contained in a fuel to electricity.

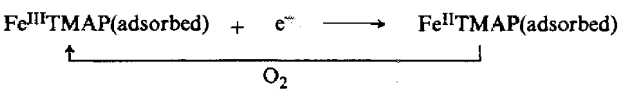
One of the most elegant approaches to the problem to date involves a cofacial cobalt–porphyrin system adsorbed on to graphite electrodes. The active porphyrin is represented in (**35**). The mechanistic scheme which has been proposed is represented schematically in equation (46), where the symbol '$Co^{III}|\ |Co^{III}$' represents one bifacial porphyrin entity in which both metal atoms are cobalt(III). The spacing of the two porphyrin rings appears critical for the effective catalytic action.[94]



(**35**)



Another approach which has been effective in achieving the four-electron reduction of dioxygen to water is based on the irreversible adsorption of iron(III) tetrakis(*N*,*N*,*N*-trimethylanilinium)-porphyrin (FeTMAP) on glassy carbon electrodes.[95] Data suggest that the dioxygen reduction is determined by a surface redox couple in a surface electrochemical catalysis mechanism (equation 47). Unfortunately, repeated scanning of the potential range results in loss of activity (10% per cycle). This is attributed to loss of porphyrin from the surface and to degradation by the intermediate H_2O_2.



(47)

Even reactions which are thermodynamically unfavoured, *e.g.* with K_{aq} as low as 5×10^{-6}, may be electrocatalytically mediated. For example, rotating platinum electrodes covered with polymerized $[Ru(4\text{-vinyl-}4'\text{-methyl-}2,2'\text{-bipyridyl})_3]^{2+}$will electrocatalytically mediate the oxidation[96] of such species as $[Ru(bipy)_3]^{2+}$, $[Ru(bipy)_2(4,4'\text{-bipy})_2]^{2+}$, $[Ru(bipy)_2(py)(MeCN)]^{2+}$, $[Ru(bipy)_2(MeCN)_2]^{2+}$ and $[Ru(bipy)_2(pyrazine)_2]^{2+}$.

(iv) Electronic devices

Considerable potential exists to design surface modified electrodes which can mimic the behaviour of electronic components. For example, a rectifying interface can be produced by using two-layer polymer films on electrodes. The electroactive species in the layers have different redox potentials. Thus electron transfer between the electrode (*e.g.* platinum) and the outer electroactive layer is forced to occur catalytically by electron transfer mediation through the inner electroactive layer.

Such bilayers can conveniently be built up by successive electropolymerization of complexes containing ligands with vinyl substituents, *e.g.* 4-vinylpyridine or 4-vinyl-4′-methyl-2,2′-bipyridyl. The films may be deposited on metallic or semiconductor electrodes (*e.g.* Pt, glassy carbon, SnO_2, TiO_2). More efficient metallation of the films is obtained by polymerization of coordinated ligand than by subsequent metallation of a preformed polymer film. An alternative to discrete films would be a copolymer with distinct redox sites, or a combination of a single polymer film with a copolymer film in a bilayer device.

The concept can be illustrated with the help of Figure 7.[97] The inner layer (redox system A) insulates the outer layer (copolymer of redox system A and B). The outer layer must be permeable

to counter ion flow as required by redox reactions of the inner layer. As the potential is scanned from negative to more positive potentials, it is seen that current can flow only at certain potentials; hence maintaining the potential at value (i) or (ii) will give a device which permits current flow in one direction only. Suitable chains of A and B are $[Ru^{II}(bipy)_2(4\text{-}VP)_2]^{2+}$ and $[Ru(bipy)_2(4\text{-vinyl-4'-methyl-2,2'-bipy})]^{2+}$ where 4-VP is 4-vinylpyridine.

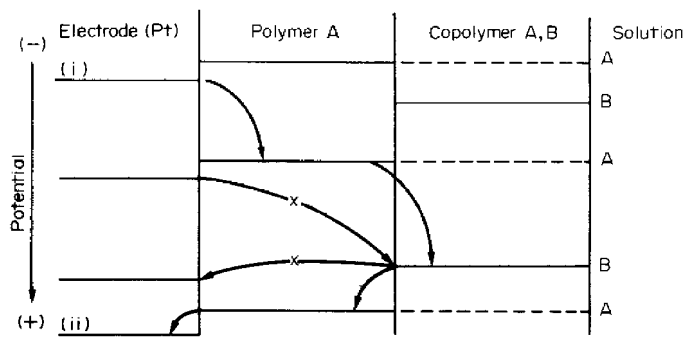


Figure 7

A variation of the concept[98] has been provided by studying electrodes coated by electrochemical polymerization of ruthenium(II)–4-vinyl-4'-methyl-2,2'-bipyridyl complexes such that the thickness of the coating can be controlled. If such electrodes are placed in contact with a solution containing *both* $Fe(Cp)_2$ and $[Ru(bipy)_2(py)Cl]PF_6$ (methyl cyanide solvent), it is found that $Fe(Cp)_2$ may be selectively oxidized with a covering of 10 monolayers. The selectivity depends on the relative permeability and diffusional characteristics of the redox reagents within the polymer film. As the film thickness builds up towards 60 monolayers, charge transfer through the film becomes the only mechanism for oxidation of the ruthenium(II) complex, but this cannot occur until the film couple is approached, when partial oxidation $Ru^{II} \longrightarrow Ru^{III}$ in the film will create an electron hopping pathway through the film. Thus with thick films the oxidation–reduction behaviour at the electrode is determined by the characteristics of the film rather than by the inherent redox couple. The film may then have properties more usually associated with devices such as diodes and transistors.

A novel approach to data storage applications involves a glassy carbon electrode with a coating of $[Ru(bipy)_2(PVP)Cl]Cl$, where PVP is poly-4-vinylpyridine. The rotating electrode oxidizes iron(II) at 640 mV [the polymer coating will inhibit iron(II) oxidation until ruthenium(II) centres are oxidized to ruthenium(III)]. If the electrode is irradiated, a photochemically mediated substitution of the chloro ligand by an aquo ligand will occur and, after this radiation, a more positive potential (740 mV) is required to oxidize iron(II). Thus if the electrode potential is held between 640 and 740 mV a 'yes'/'no' device is possible since irradiation will eliminate the flow of current.[99]

A rather general problem is that the devices indicated above are usually too slow to be of immediate practical application but clearly the opportunity to develop more research is enormous.

(v) Solar energy conversion

The harnessing of solar energy as a seemingly inexhaustible energy source is attractive but many problems have yet to be solved before efficient conversions of solar energy are available. Two thrusts in the research are relevant to this chapter. One possibility is to generate photoelectricity by illumination of a semiconductor electrode in contact with an appropriate solution redox couple which lies within the band gap of the semiconductor. Schematically, this is represented in Figure 8 following Wrighton.[40]

Alternatively, the photoelectrode may be used to generate fuel, the photoelectrolysis of water being an obvious target. In this case the excited electron–hole pairs must have sufficient reducing and oxidizing powers to drive the O_2/H_2O and H_2O/H_2 half cells.

A practical problem with *n*-type semiconductors is that photoanodic oxidation can quickly render the system useless; surface derivatization was seen as a way round the problem. A range of silanated ferrocenes was used to derivatize silicon electrodes with a remarkable increase in the stability of the photocurrent as a function of time.[100] Illumination causes the oxidation of surface bound ferrocene which, in turn, oxidizes a redox species such as $[Fe(CN)_6]^{4-}$ in solution.

Another approach has been to use a photogalvanic cell with a rotating optically transparent SnO_2 electrode. Light is used to drive a redox reaction in solution, *e.g.* equation (48):[42]

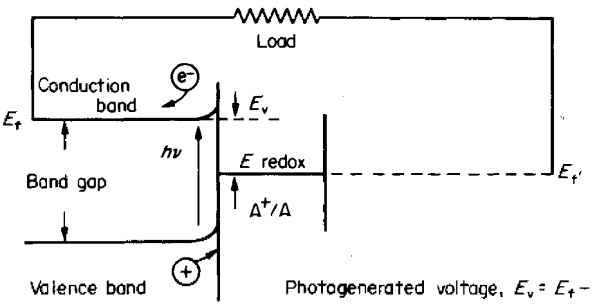


Figure 8 Photovoltaic cell based on an *n*-type semiconductor

$$\left[Ru^{II}(bipy)_3\right]^{2+} \xrightarrow{h\nu} \left[Ru^{II}(bipy)_3^*\right]^{2+}$$

$$\left[Ru^{II}(bipy)_3^*\right]^{2+} + Fe^{III} \longrightarrow \left[Ru^{III}(bipy)_3\right]^{3+} + Fe^{II} \quad (48)$$

The above system is in fact not attractive in practice, mainly because rate constants are significantly greater than is desirable.

(vi) Metallization

It is interesting to conclude this section with an example that, in a sense, brings the chapter full circle. The metallization of plastic materials used as metal substitutes is a process with actual and future commercial potential. Usually, plastics are plated after appropriate sensitization by an electroless process which involves reduction of metal ions (*e.g.* Ni^{2+}, Cu^{2+}) by chemical rather than electrical means.[19] There seems no reason why the reducing agent should not be incorporated in the polymer and Murray and his collaborators[101] have demonstrated that copper, silver, cobalt and nickel may each be electrodeposited on to films of $[poly\text{-}Ru(bipy)_2(4\text{-}vinylpyridine)_2]^{2+}$ coated on to platinum electrodes. The metal reductions are mediated by the Ru^I and Ru^0 states of the polymer.

57.4 GENERAL CONCLUSION

The unifying theme of this chapter has been chemistry at the electrode surface, an approach which it is hoped has introduced some cohesion to the material selected for coverage. The constraint that coordination chemistry should be involved has been observed but, even within this constraint, no attempt has been made to be totally comprehensive in the coverage of the literature in the sense that would be expected of a review article. Rather a small scale map has been drawn and those now requiring a larger scale map of particular areas are referred in the first instance to those general texts[1,2,4,8,19] and review articles[40–43,67] cited.

It is clear that the field of chemically modified electrodes has a great future. Commercial success is already evident within the chlor-alkali industry where dimensionally stable TiO_2/RuO_2 derivatized electrodes have replaced graphite and produced significant savings in the consumption of electric power. Dispersed electrodes will attract much attention in the future. One goal might be particles of a semiconductor modified in different ways on opposite sides to drive the H_2O/H_2 and O_2/H_2O half cell reactions. The coordination chemist does not have a unique role to play since this is very much a multidisciplinary area of research; however, it would be surprising if no major breakthrough of the future were based on the redox chemistry of coordinated metal ions.

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58

Dyes and Pigments

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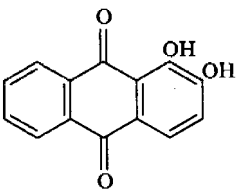
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58.1 INTRODUCTION

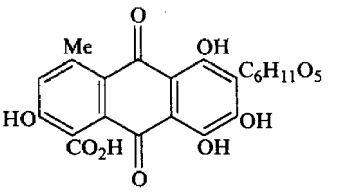
Man has been fascinated by colour since time immemorial, as witnessed by the coloured representations of animals with which the early cavemen adorned the walls of their dwellings. This fascination persisted through the Egyptian, Greek and Roman eras and remains undiminished right up to the present day. From the very earliest times man desired to colour the fabrics he possessed and initially he turned to Nature for the materials with which to accomplish this. The origin of organic dyes and pigments is lost in antiquity but both sprang from the use of natural products such as Brazilwood, logwood, kermes, lac-dye, cochineal, Persian berries and madder. Many of these emerged as useful dyestuffs because they could be applied by one of the earliest dyeing processes. This, to become known as the mordant method, depended upon the formation of insoluble metal salts or complexes within the fibre.

In the early days, dyeing was not a science but an art or a craft and could hardly be otherwise. Frequently dyeing processes involved treating the fibres with mixtures of 'dyes' of animal or vegetable origin and varying proportions of clay, earth, ashes, slate dust, powdered brick and various gums, all with the objective of achieving the best and most consistent result. Gradually it came to be recognized that the results obtained with certain dyestuffs and clay materials could be improved by replacing the latter by alum and other metallic salts and mordant dyeing was born. In this the cloth to be dyed was impregnated with a solution of a soluble salt of a metal such as aluminum, iron, chromium or tin and the insoluble metal hydroxide was precipitated within the fibre. This 'mordanted' fibre was then treated with a solution of a naturally occurring colouring matter capable of forming an insoluble complex with the mordant. Various natural colouring matters were used which differed widely in chemical structure. All, however, contained a chelating system. The most important was alizarin (**1**), obtained from madder root, which gave a beautiful bluish red shade with an aluminum mordant and had excellent fastness properties. In 1868 some

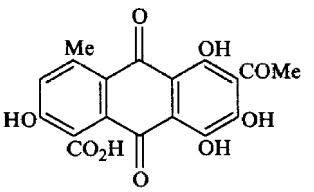
400 000 acres of land were given up to the cultivation of the madder root and world production was 70 000 tons a year. It was an industry in itself, but was destroyed almost overnight when Graebe and Lieberman identified the principal colouring matter as 1,2-dihydroxyanthraquinone and were successful in making it artificially. Other naturally occurring dyes containing the 1-hydroxyanthraquinone chelating system are cochineal and kermes, the active constituents of which are carminic acid (**2**) and kermesic acid (**3**), respectively. Both are obtained from insects, the former from the female of the species *Coccus cacti*, which lives on cacti in Mexico, and the latter from *Coccus ilicis*, which infests the kermes oak. About 200 000 insects are required to produce 1 kg of cochineal but it was used in the UK at least until 1934 with a tin mordant for dyeing the Guards' tunics and the piping on postmen's trousers!



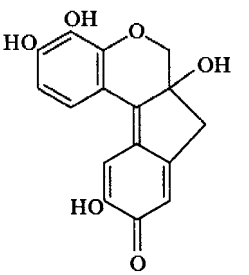
(1)



(2)



(3)



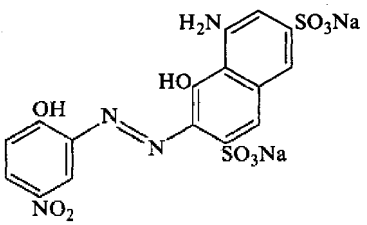
(4)

The success of logwood, from the heartwood of the tree *Haematoxylan campechianum L* found in Central America, as a black dyestuff also depended on complex formation. The active constituent of logwood is the chroman hematein (**4**), which is itself red. When applied with a chromium mordant, however, logwood gave black shades and held the premier position for blacks and blues until the late 1890s, by which time synthetic dyes accounted for some 90% of the dyes used.

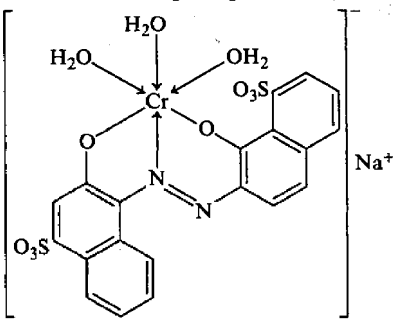
The principal characteristic of a *pigment* which distinguishes it from a *dyestuff* is that it is substantially insoluble in the medium in which it is used. There are many other distinctions of vital technical importance but, for the present purpose, this very simplified differentiation is adequate. The development of organic pigments was slower than that of organic dyestuffs but sprang from the use of crude inorganic materials to 'fix' dyestuffs of natural origin within fibres. It was recognized that natural dyes such as alizarin formed highly coloured insoluble substances with clays. These could be incorporated into oily or resinous materials and used for decorative purposes; hence *pigment* from the Latin *pingere*, to paint. As methods of dyeing became better understood, so the clays were replaced by metal salts such as alum and the foundation for the development of modern metal complex organic pigments was firmly established. The advent of synthetic dyes, particularly the all important azo series, did nothing to diminish the importance of metal complex formation in dyeing. It continued to provide, through the mordant method, solutions to problems such as the colouring of fabrics with dyestuffs which had no natural affinity for the fibre in question and the achievement of good fastness to washing and light.

With the wide variety of azo dyes available it became unnecessary to use different metals to obtain different colours and salts of chromium rapidly displaced those of other metals since 'chromed' azo dyes were found to have the best fastness to light and washing, particularly on wool. Three principal dyeing methods were employed, the chrome mordant, the afterchrome, and the metachrome processes. In the first, the wool was treated with sodium dichromate and an agent such as oxalic acid to reduce chromium to the trivalent state. The wool was then dyed with an azo dyestuff, *e.g.* (**5**), which formed a chromium complex on the fibre. The process was effectively reversed in the afterchrome method in which the wool was first dyed with a suitable azo dyestuff, then treated with sodium dichromate in the same or a fresh dyebath. In the metachrome process the dyeing was carried out in a single bath which contained the dyestuff, sodium dichromate and

ammonium sulfate. This method was clearly advantageous from the point of view of the dyer but had limited application since it required dyes which had affinity for wool in a dyebath which was only slightly acidic, were not oxidized by chromate and were not precipitated by chromium salts.



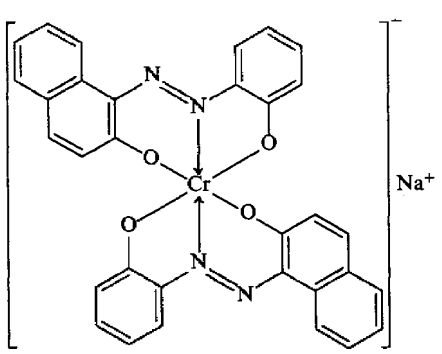
(5)



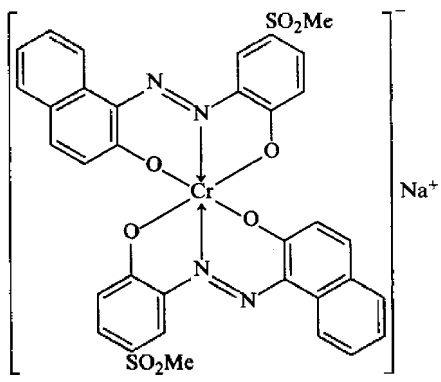
(6) Neolan Blue 2G (Ciba)

The most obvious problem common to all three methods from the point of view of the dyer was the achievement of consistent results since a change of shade occurs on complex formation. Throughout the history of the synthetic dyestuffs industry one aim of the chemist has been to simplify the work of the dyer by improving dyeing methods and making possible the achievement of consistent results in an economic manner. In the case of metal complex dyestuffs the first step towards achieving this came as long ago as 1919 when the Swiss firm Ciba and IG in Germany introduced their Neolan and Palatine Fast ranges of 1:1 chromium complex azo dyestuffs for wool, *e.g.* (**6**). The application of these dyes to wool requires a strongly acidic dyebath which results in appreciable damage to the wool and serious impairment of its soft handle. Nevertheless, their introduction marked a major advance in the field of metal complex dyestuffs since the dyeing operation was carried out in a single bath and shades could be matched without difficulty.

In the late 1930s, IG began to place on the market a limited range of 2:1 chromium complex dyes, *e.g.* (**7**), for synthetic polyamide fibres, an application for which they were particularly suitable since they could be applied from a near neutral dyebath. Their aqueous solubility was, however, very limited and all were applied as dispersions, restricting their value as dyestuffs for wool. In an attempt to overcome this problem, similar 2:1 chromium complexes derived from azo dyes containing sulfonic or carboxylic acid groups were examined. These had more than adequate water solubility but proved to be exceptionally sensitive to natural variations in the fibre and gave unlevel dyeings. A solution was discovered by the Swiss firm Geigy whose Irgalan range of 2:1 chromium complex dyes, *e.g.* (**8**), for wool was introduced in 1949. These were derived from azo dyes containing non-ionic hydrophilic substituents, such as methylsulfonyl, sulfonamide or acetylamino groups, which conferred adequate water solubility on the chromium complexes without adversely affecting dyeing properties. Further, they could be applied to wool from neutral or weakly acid dyebaths, minimizing damage to the fibre, and gave dyeings having excellent fastness to washing and light. The importance of this development is illustrated by the rapidity with which other manufacturers introduced comparable ranges of neutral dyeing 2:1 chromium complex dyestuffs under the names *Cibalan* (Ciba), *Lanasyn* (Sandoz), *Isolan* (Bayer), *Ortolan* (BASF), *Capracyl* (Du Pont) and others.



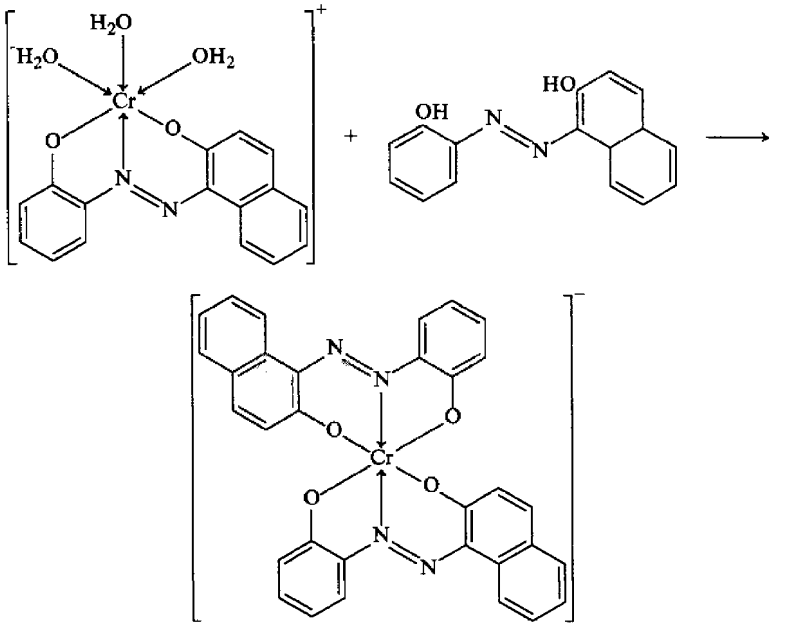
(7) Perlon Fast Violet BT (IG)



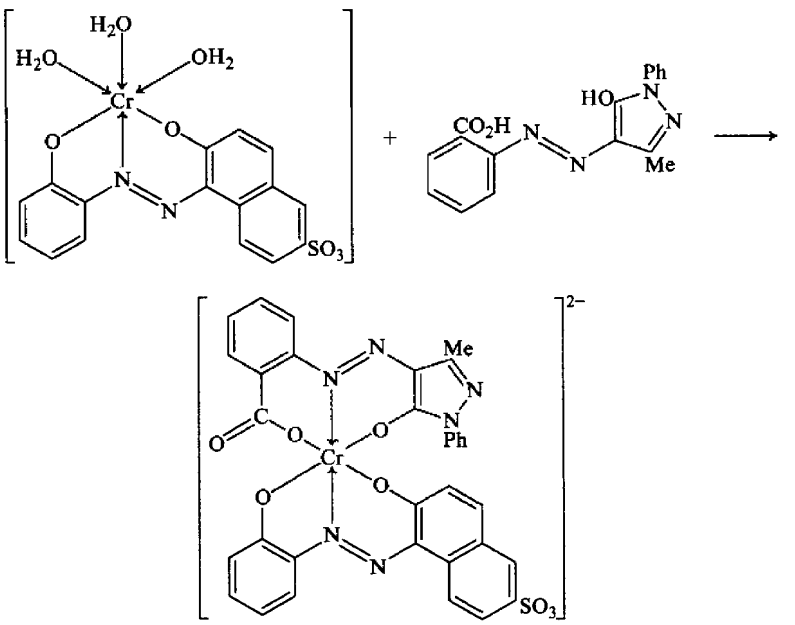
(8) Irgalan Brown Violet DL (Geigy)

The next milestone in the history of chromium dyes for wool arose from the observation that 1:1 chromium complex dyestuffs react with a second molecule of a metal-free, tridentate azo compound to give the 2:1 chromium complex. If the second dyestuff is the same as that from which

the 1:1 chromium complex was derived, a symmetrical 2:1 chromium complex (**9**) is produced. If, however, a 1:1 chromium complex reacts with a molecule of a different tridentate azo compound, an unsymmetrical 2:1 complex (**10**) results. The range of available shades can be extended by using such mixed structures. Further, it is possible to prepare unsymmetrical 2:1 chromium complex dyestuffs from two azo compounds only one of which contains a sulfonic acid group. In this way, relatively cheap products having good solubility have been obtained which give level dyeings on wool from neutral dyebaths with negligible damage to the fibre. Fastness properties are good and dyes of this type occupy a leading position for wool.



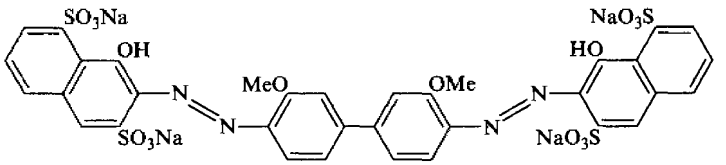
(**9**)



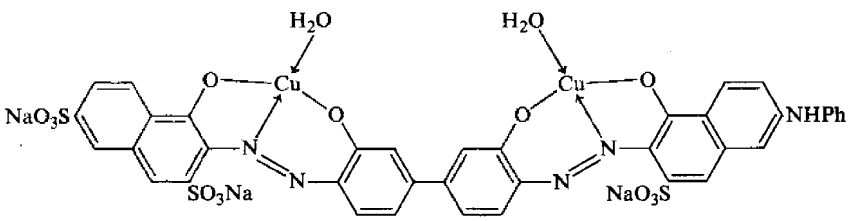
(**10**)

Both 2:1 chromium and cobalt complex azo dyestuffs have little or no affinity for cellulosic fibres and until the early 1960s their use was restricted to wool and nylon. With the introduction by ICI of their Procion range of fibre-reactive dyes, however, their use was extended to cellulosic fibres on which they give prints having excellent fastness to light and wet treatments. Before that time the development of metal complex dyes for cellulose had followed a similar pattern to that of the development of such dyes for wool but, in this case, the most important metal was copper. Early work in this field has been reviewed by several authors.[1] The after-treatment of dyeings on cotton obtained from dyestuffs such as (**11**) with copper salts was used for many years to improve fastness

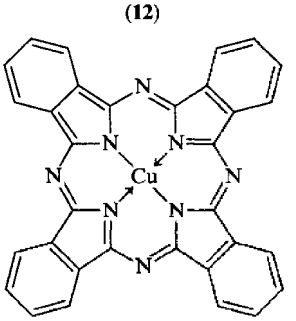
to light and washing. On repeated washing, however, the effect was lost: it was gradually recognized that this was because of the low stability of the copper complex formed by (**11**) and that improvements could be obtained by using dyes containing the *o,o′*-dihydroxydiarylazo system rather than the *o*-hydroxy-*o′*-methoxydiarylazo system in (**11**). Water-soluble copper complexes of *o,o′*-dihydroxydiarylazo dyes were first prepared by SCI (now Ciba-Geigy) in 1915 and they could be applied[2] to cotton in the same way as ordinary direct dyes. Following that observation, a large number of water-soluble copper complexes of tridentate azo dyestuffs (*e.g.* **12**) were marketed. Such dyes were usually very fast to light but had only moderate wash fastness. This was overcome with copper complex dyestuffs containing fibre-reactive groups, such as some members of ICI's Procion ranges, which give dyeings on cellulose having excellent fastness to light and to wet treatments.



(**11**)



(**12**)



(**13**)

So far as metal complex pigments are concerned, the phthalocyanines must occupy the prime position. Phthalocyanine itself was discovered by von Braun in 1907 and copper phthalocyanine some 20 years later by de Diesbach. It was, however, left to Dandridge, Drescher, Dunsworth and Thomas of Scottish Dyes Ltd. (later ICI) to realize the potential of the copper complex as a pigment. They first noticed the presence of a coloured impurity in phthalic anhydride prepared by the reaction of ammonia with molten phthalimide in an enamelled iron vessel in which the enamel was damaged. The coloured impurity proved to be iron phthalocyanine, the iron coming from the reaction vessel. Subsequently copper phthalocyanine (**13**) was shown to possess even better properties as a pigment and today copper phthalocyanine and its halogenated derivatives are probably the most important pigments employed in high quality blue and green automotive finishes.

Dyes and pigments are effect chemicals and it is vital that their technical properties are appropriate for the market for which they are intended. It is immediately obvious that features such as shade, strength and brightness of hue are of prime importance in dyes and pigments but many other requirements must be met by successful products. In the case of dyestuffs, for example, vastly different properties are required for the dyeing of cotton, wool and the three main man-made fibres — nylon, polyester and polyacrylonitrile. Further, the colouration produced should be permanent throughout the useful life of the dyed material, requiring that the dyestuff be fast to light, washing, dry cleaning, heat and various other agencies. Similarly, pigments must be easily dispersed in the medium in which they are employed and must satisfy a whole range of technological criteria.

The colour of dyes and pigments stems from the chromogens upon which they are based but many of the other properties are achieved through the introduction of appropriate substituents into the parent chromogen. For example, high wet-fastness on cotton is obtained by the intro-

duction of the dichlorotriazinyl group into a dyestuff which then reacts with cellulose under alkaline conditions to form a covalent bond between the dyestuff and the cellulose.

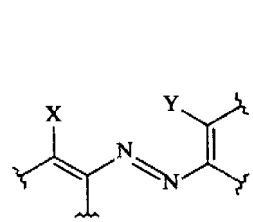
So far as chromogens are concerned, most of those presently employed in dyes and pigments had been discovered by the end of the 19th century and since then very few new chromogens have been added to the range of available dyestuffs, a notable exception being copper phthalocyanine. Similarly, most major advances in metal complex dyestuffs in which the metal may be regarded as part of the chromogen, for example the 2:1 chromium and cobalt complexes of tridentate azo compounds, had been made when this subject was reviewed in the late 1960s.[3b] Thus, whilst a large number of publications, particularly patents, have appeared since that time, most have related to the achievement of desirable technical effects by modification of dyestuff structures rather than to coordination chemistry. For example, in the field of 2:1 chromium complexes of tridentate azo compounds, many publications relate merely to building up new complexes from previously known dye ligands using known methods for their preparation.

It is not the purpose of this chapter to present a detailed account of the history and technology of metal complex dyes and pigments since many comprehensive reviews are available.[3,3a–d] The discussion has, therefore, been limited to those aspects of the subject which centre on coordination chemistry rather than dyestuff and pigment technology, with special reference to the effects of coordination on ligand reactivity. This brief introduction will serve to demonstrate that coordination chemistry has figured prominently in the development of the dyes and pigments industries from the earliest times. Further, it is at least in part due to the large amount of research in these industries that many of the advances in coordination chemistry since its recognition by Werner have been made.

This chapter is concerned with dyes and pigments which are complexes of azo, formazan, azomethine, nitroso, anthraquinone and phthalocyanine ligands. Many of these compounds find important applications in other fields, particularly colour photography and reprography, analysis, catalysis, biology, and some modern high technology industries such as electronics. These applications are described in other chapters of this volume.

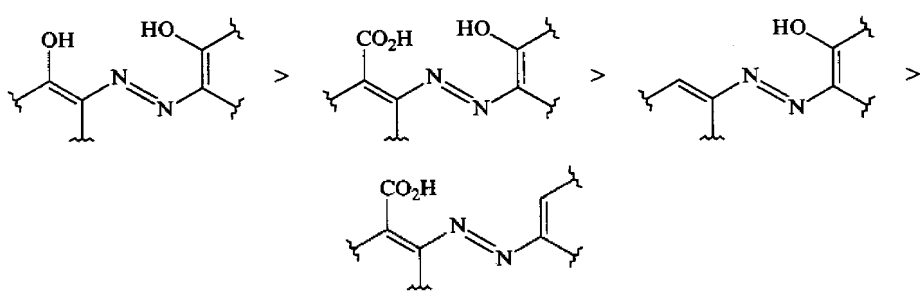
58.2 METAL COMPLEXES OF AZO COMPOUNDS

Metal complex azo dyes and pigments may be conveniently divided into two classes: those in which the azo group is involved in coordination to the metal and those in which it is not. The former are by far the more important and are derived from chelating diarylazo compounds (**14**) having at least one donor function *ortho* to the azo group. For obvious reasons, only those metal complex dyes stable under dyebath conditions and towards agencies to which the dyed material may be subsequently exposed are used commercially. The stability of the complexes depends upon factors including the size of the chelate ring, the formation of annelated chelate rings, the basicity of the ligand, and the nature of the metal.



(14)

X	*Y*	
H	OH	bidentate
H	NH_2	
OH	OH	tridentate
OH	NH_2	
CO_2H	OH	



(15)

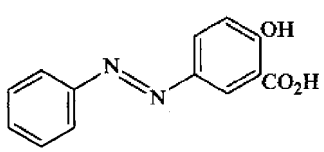
A decisive factor in the formation of a chelate ring is the number of atoms involved in ring formation: chelates with five- or six-membered rings are the most stable; this criterion is met by

the compounds (**14**). Similarly, annelation of chelate rings results in enhancement of the stability of complexes. Not surprisingly, therefore, the metal complexes formed by the tridentate azo compounds are more stable than those formed by the bidentate ligands. As a rule the most basic ligand forms the most stable complex and the most acidic the least stable complex. In accord with these principles the relative stabilities of metal complexes of bi- and tri-dentate azo compounds follow the general sequence (**15**). In practice, only metal complexes of tridentate azo compounds find wide commercial application.

Chromium and cobalt are the metals most commonly used in dyestuffs for polyamide fibres and leather because of their kinetic inertness and the stability of their complexes towards acid. Since the advent of fibre-reactive dyestuffs, chromium and cobalt complexes have also found application as dyestuffs for cellulosic fibres, particularly as black shades of high light-fastness. Copper complexes are of more importance as dyes for cellulosic fibres and are unsuitable for polyamide fibres because of their rather low stability towards acid treatments.

The importance of such metal complexes stems principally from their very high light-fastness, attributed[4] to protection of the azo group by the metal against attack by, for example, singlet oxygen. This explanation appears eminently reasonable since one result of a ligand becoming coordinated to a metal is that it becomes less susceptible to electrophilic attack. This is also manifested in the generally good fastness of such dyestuffs to oxidizing agents such as sodium hypochlorite. The penalty paid for the improvement in these and other technically important properties is that such metal complexes are generally duller in shade than the parent azo compounds. This dulling effect and the associated bathochromic shift does not arise from the forbidden $d \rightarrow d$ transitions of the metal itself. These are so weak ($\varepsilon_{max} \ll 10^3$) that they are completely swamped by the permitted, intense $\pi \rightarrow \pi^*$ transitions of the chromogen (ε_{max} *ca.* 25 000). The colour change is the result of chelation of the major donor groups, azo, X and Y (**14**), to the metal, which produces a major perturbation of the π-electron distribution.

Metal complex azo dyestuffs in which the azo group is not involved in coordination at the metal are derived from azo compounds (*e.g.* **16**) based on coupling components such as salicylic acid, 8-hydroxyquinoline and salicylaldehyde. In general, metal complexes of this type are brighter in hue than those in which the azo group is involved in coordination to the metal, little shade change occurs on complex formation and there is little or no enhancement of the light fastness of the dyestuff. The principal reason for the introduction of dyestuffs of this type was their relatively good fastness to washing. This is now achieved by other means and dyes of this type are of little or no commercial importance.

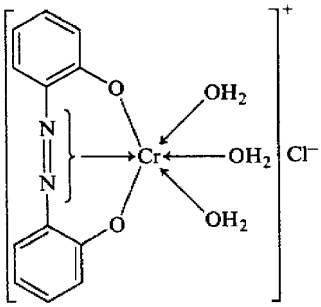


(**16**)

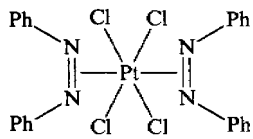
58.2.1 Nature of Bonding by the Azo Group

The donor properties of the azo group are weak and its involvement in coordination to a metal ion was originally inferred from the observation that whereas those azobenzenes having a hydroxy or amino group *ortho* to the azo group form metal complexes, those having such groups in *meta* or *para* positions do not. However, it was not clear whether the bonding between the azo group and the metal involved the sp^2 lone pair of electrons of one of the nitrogen atoms or the π-electrons of the azo group, and as recently as 1952 this uncertainty was indicated[5] by a bracket enclosing the entire azo group (**17**). In 1947, Werner[6] proposed a π-bonded structure (**18**) for a compound obtained[7] by the interaction of azobenzene and platinum(IV) chloride but this was subsequently shown[8] to be a salt derived from hydrazobenzene and hexachloroplatinate(IV).

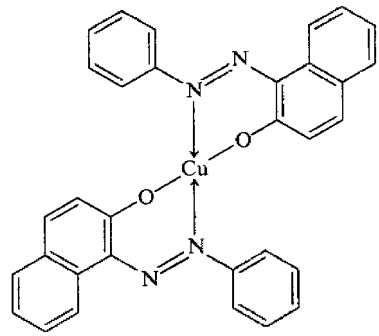
Later workers succeeded in isolating silver and palladium complexes of azobenzene[9] and 5,6-benzocinnoline,[10] which may be compared with *cis*-azobenzene. No information on their structures is available but their existence was taken to demonstrate coordination of the azo group in the absence of other donor groups in the molecule. The mode of coordination of the azo group to a metal ion was not fully resolved until X-ray data on several metal complex azo compounds established that only one nitrogen atom of the azo group is involved in bonding to the metal. In the case of the copper complex[11] (**19**) of 1-phenylazo-2-naphthol the β-nitrogen atom of the azo group is bonded to the metal which forms part of a six-membered chelate ring.



(17)



(18)

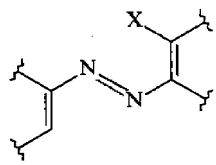


(19)

58.2.2 Bidentate Azo Compounds

58.2.2.1 Medially metallized types

In general, the stability towards acids and alkalies of metal complexes of bidentate diarylazo compounds (**20**) is inadequate for them to find application as dyestuffs and only a limited number are used as pigments. They are, however, of some historical interest and their relative simplicity compared with metal complexes of tridentate azo compounds makes them useful models for the study of the latter, technologically important class. They are, therefore, considered here in some detail.

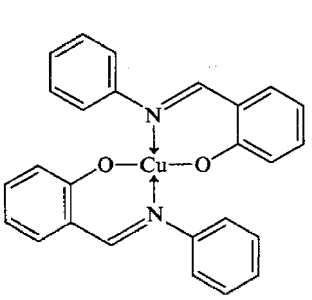


(**20**) X = OH, NH_2

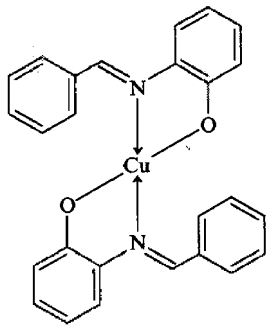
The first substantially pure complex of a bidentate diarylazo compound appears to have been prepared as long ago as 1893, when Caberti[12] obtained a brown pigment by the interaction of 1-(4-nitrophenylazo)-2-naphthol and copper salts. Copper, nickel and cobalt complexes of *o*-hydroxy- and *o*-amino-diarylazo compounds were subsequently prepared by a number of workers[13,13a,b] but it was not until the classical work of Drew and his coworkers[14] that the structures of these complexes were established with any degree of certainty. These workers confirmed that both classes of azo compound reacted with copper, nickel, and cobalt(II) salts to give neutral complexes having 2:1 stoichiometry in which a proton was lost from each molecule of the azo compound. Comparison of the copper complex of *o*-hydroxyazobenzene with those of the copper complexes of *N*-phenylsalicylaldimine (**21**) and benzylidene-*o*-aminophenol (**22**) led them to propose structure (**23**). The structure was subsequently confirmed by X-ray crystal structure determinations on the copper [11] and nickel[15] complexes of 1-phenylazo-2-naphthol. The copper complex consists of two molecules of 1-phenylazo-2-naphthol centrosymmetrically disposed about the central copper ion, the two oxygen atoms and the β-nitrogen atoms of the azo groups forming a square (**24**). The molecule as a whole is not planar, the azo group lying out of the plane of the β-naphthol nucleus and that of the benzene ring. This is indicative that the ligand is coordinated to the metal in the azo rather than the hydrazone form (Section 58.2.3.2).

Despite the incontrovertible evidence regarding the structure of copper and nickel complexes of *o*-hydroxydiarylazo compounds, confusion remained with regard to their cobalt complexes. Thus some workers[13a,b,14,16] reported the isolation of complexes having 2:1 stoichiometry whilst others[5,17] reported 3:1 stoichiometry. The oxidation state of the cobalt was also in dispute. The situation was clarified[18] when more modern techniques were employed to study the reaction of 1-phenylazo-2-naphthol and related compounds with various cobalt salts and complexes. The results of this work are summarized in Scheme 1.

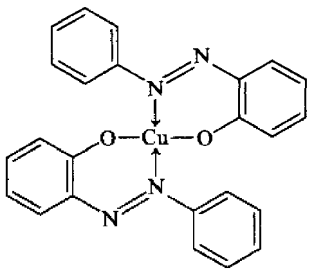
Several points are noteworthy: first, the conversion of the 2:1 cobalt(II) complex into the 3:1 cobalt(III) complex in the presence of mineral acid and atmospheric oxygen, which no doubt accounts for the variable results obtained by earlier workers; and second, the isolation of the complexes of formula $[(LH)_2Co^{II}X_2]$ and their facile conversion into the complexes of formula $[L_2Co^{II}]$. The former were considered to be octahedrally coordinated cobalt(II) complexes on the basis of magnetic and conductance measurements and represented the first examples of metal



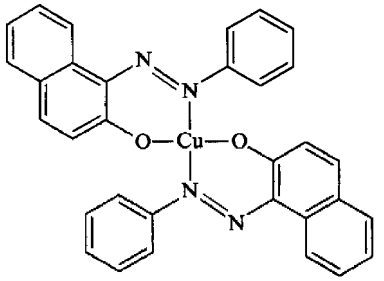
(21)



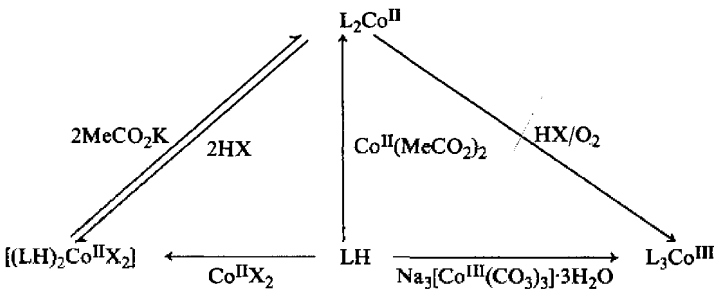
(22)



(23)



(24)

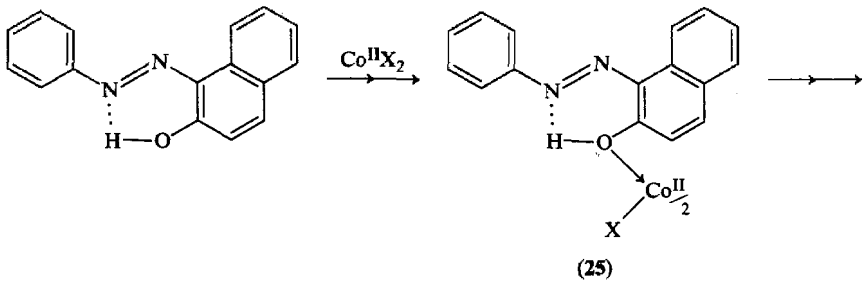


LH = 1-phenylazo-2-naphthol; X = Cl, Br

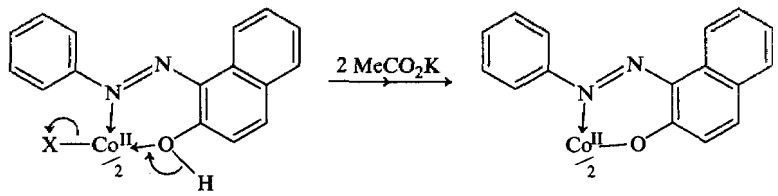
Scheme 1

complexes of *o*-hydroxydiarylazo compounds in which no proton loss from the ligand had occurred. Implicit in this conclusion is the fact that *o*-hydroxydiarylazo compounds are capable of functioning as bidentate ligands *per se*.

These results led to an acceptable mechanism (Scheme 2)[19] for the formation of neutral 2:1 cobalt(II) complexes of *o*-hydroxydiarylazo compounds by the interaction of the latter and divalent cobalt salts. *o*-Hydroxydiarylazo compounds are very weak acids ($pK_A \approx 10$)[20] and it is unlikely that they are ionized appreciably under the conditions typically employed for their conversion to metal complexes. The first step in the reaction is, therefore, seen as coordination of the un-ionized ligand to the metal ion. *o*-Hydroxydiarylazo compounds exist in solution as an equilibrium mixture of strongly hydrogen-bonded azo and hydrazone forms (Section 58.2.3.2), the position of the equilibrium being determined by several factors, including the structure of the azo compound, solvent, *etc.* It is not clear which tautomer is involved in the first step in the reaction sequence but this is seen as involving the oxygen atom of the ligand (**25**). Chelation then leads to the hexa-coordinate, neutral complex (**26**). Treatment of the latter with potassium acetate results in the loss of the elements of hydrogen halide to give the neutral, tetrahedral 2:1 cobalt(II) complex (**27**). It is apparent from this that the chelated ligand is a stronger acid than is acetic acid (pK_A 4.75). Not surprisingly, therefore, (**27**) is the product when 1-phenylazo-2-naphthol reacts with cobalt(II) acetate. Unfortunately the pK_A value of the coordinated 1-phenylazo-2-naphthol was not reported but, clearly, it is markedly lower than that of the free azo compound. This is a good example of the remarkable enhancement of the acidity of a ligand as a result of its becoming coordinated to a metal ion, which is of considerable importance in problems encountered in the manufacture of chromium complexes of tridentate metallizable azo compounds (Section 58.2.3.1(i)(a)).



(25)



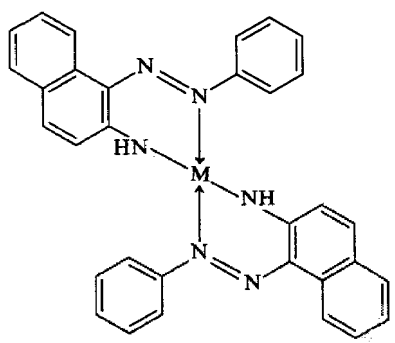
(26) (27)

+ 2KX + 2$MeCO_2H$

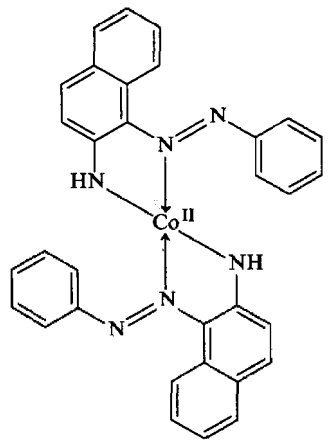
Partial structures; X = Cl, Br

Scheme 2

Drew[14] proposed structures (**28**) for the copper, nickel and cobalt complexes of 1-phenylazo-2-naphthylamine which were analogous to those of the corresponding complexes of 1-phenylazo-2-naphthol. Doubts regarding this formulation have, however, been raised by the observations[18] that whereas the 2:1 cobalt(II) complex of 1-phenylazo-2-naphthol has tetrahedral geometry, the 2:1 cobalt(II) complex of 1-phenylazo-2-naphthylamine has square planar geometry. These assignments were made on the basis of magnetic measurements and no X-ray structural information is available. They have, however, been used to support the suggestion that the α-nitrogen atom of the azo group is involved in the coordination of 1-phenylazo-2-naphthylamines (**29**). Complexes of this type have no practical application as dyes or pigments but considerable theoretical significance, since their formation apparently involves the loss of a proton from a primary aromatic amino group. This is discussed in more detail in Section 58.2.3.2.



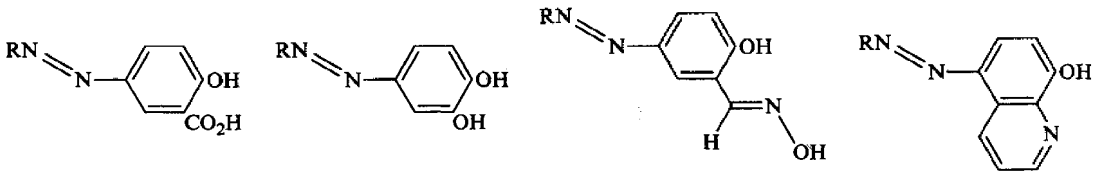
(**28**) M = Cu^{II}, Ni^{II}, Co^{II}



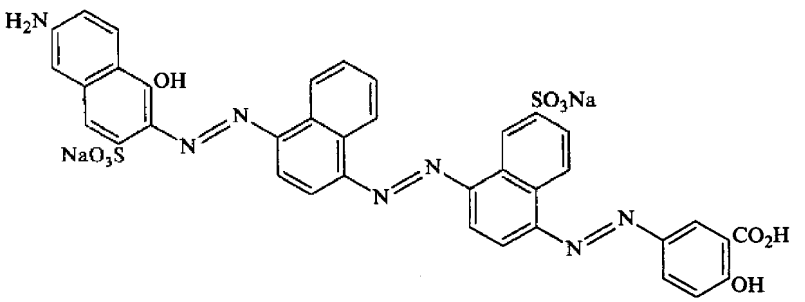
(**29**)

58.2.2.2 Terminally metallized types

Terminally metallizable dyes (**30**) are obtained by the interaction of a diazonium salt and a coupling component containing a chelating system, for example salicylic acid, catechol, salicylaldoxime or 8-hydroxyquinoline, and their coordination chemistry is typical of these compounds. Such dyes were rarely used as preformed metal complexes but were usually applied to cotton and then converted to their copper complexes on the fibre to improve their fastness to wet treatments. A typical example is the blue dyestuff (**31**).

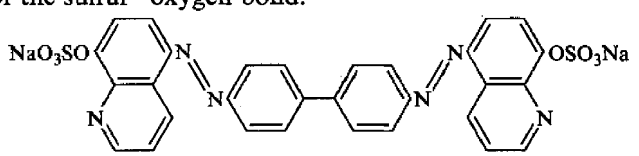


(30)

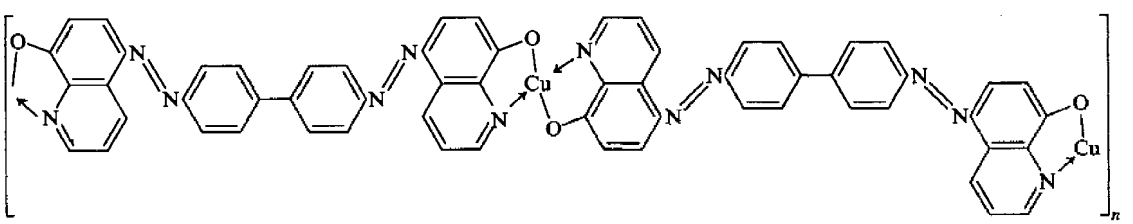


(31)

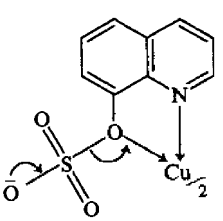
Dyes of this type have been superseded by fibre-reactive dyestuffs which have excellent fastness to washing as a result of the formation of a covalent bond between the dyestuff and the cellulosic substrate and are considerably brighter in hue. Despite the fact that terminally metallizable dyes are no longer of commercial interest, one phase in their development affords a further example of the modification of the properties of a ligand as a result of its becoming coordinated. Thus it was discovered[21] that bisazo dyes such as (**32**) gave dyeings having excellent wash-fastness when applied on cellulosic fibres in conjunction with an aftertreatment with a copper salt. The dyestuffs derived their water solubility from the sulfate ester groups which were rapidly hydrolyzed in the presence of copper salts. The hydrolyzed dyestuff was not only insoluble in water but also formed a polymeric copper complex (**33**) within the structure of the fibre which endowed it with remarkable fastness to washing. In the copper(II) ion-catalyzed hydrolysis of 8-hydroxyquinoline sulfate, Hay and Edmonds[22] concluded that the intermediate formation of a copper(II) complex such as (**34**) promoted cleavage of the sulfur–oxygen bond.



(32)



(33)

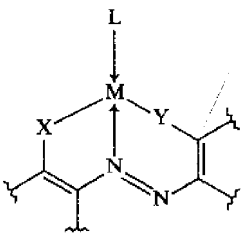


(34)

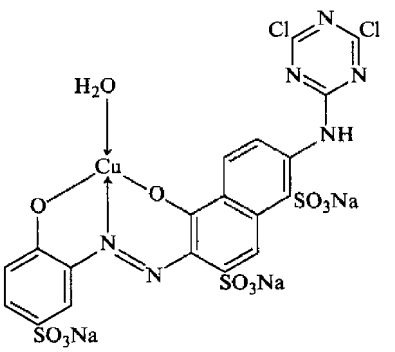
58.2.3 Tridentate Azo Compounds

Complexes derived from medially metallizable, tridentate azo compounds represent the single most important class of metal complex dyestuffs in commercial terms. Some indication of this is afforded by the fact that in 1983 the world consumption of premetallized dyes of this type was of the order of 20000 tons.

The most important azo compounds employed in the manufacture of dyes of this type are those containing the *o,o'*-dihydroxyazo-, the *o*-hydroxy-*o'*-carboxyazo- and the *o*-hydroxy-*o'*-amino-diarylazo systems. It is well established[3,3a–c] that these form four-coordinate copper and nickel complexes (**35**) in which the coordination sphere of the metal can be completed by a variety of neutral ligands. In both cases the light-fastness of the parent azo compound is improved as a result of complex formation but the nickel complexes are insufficiently stable towards acid to be of commercial interest as dyestuffs. The history of copper complexes has already been discussed (Section 58.1) and will not be considered further here, although it is worthy of mention that currently the most important copper complex dyestuffs are those containing fibre-reactive systems, *e.g.* (**36**), for application on cellulosic fibres.



(**35**) X = CO_2, O; Y = O, NH; M = Cu^{II}, Ni^{II}; L = H_2O, NH_3, pyridine, *etc.*



(**36**) Procion Rubine MXB

Much more important commercially are the 2:1 chromium(III) and 2:1 cobalt(III) complexes of tridentate azo compounds, which find a wider application, particularly as dyestuffs for wool, polyamide fibres and leather. These have been the subject of reviews[23,24] which discuss their dyeing properties in detail. The patent literature on metal complex dyes of these types is vast but since this relates principally to the achievement of specific, desirable technical effects by appropriate substitution of the azo compounds it will not be considered in detail here. Rather will the emphasis be placed upon those aspects of dyestuffs of this type which are of general interest in the context of their coordination chemistry and, more particularly, on those areas where uncertainties exist or conflicting results have been reported.

58.2.3.1 Methods of preparation

(i) Chromium complexes

It has already been stated that chromium complexes of tridentate metallizable azo compounds occupy their position as the single most important class of metal complex dyestuffs because of their high stability. It should be noted, however, that in this context the term stability is not used in the thermodynamic sense but relates to the kinetic inertness of the complexes.[25] Octahedral chromium(III) complexes have a d^3 electronic configuration and the ligand field stabilization energy associated with this is high.[26] Ligand replacement reactions involve either a dissociative

(S_N1) or an associative (S_N2) mechanism requiring the formation of five-coordinate or seven-coordinate intermediates, respectively, both of which lead to a considerable loss in stabilization energy.[27] Hexacoordinate d^3 chromium(III) complexes are, therefore, very resistant to distortions of these types with the consequence that rates of ligand replacement reactions are slow. This is a highly desirable situation so far as the chromium complex dyestuffs are concerned but leads to problems in their synthesis since the starting point is traditionally a chromium salt containing the hexaaquachromium ion which is itself kinetically inert.[28] The consequence of this is that tridentate azo compounds react very slowly with aquated chromium salts in aqueous medium and in many cases the reaction fails to go to completion unless large excesses of chromium are used. This is commercially very undesirable since it results in long plant occupation times, high energy requirements and, in some cases, the use of pressure equipment. Consequently the dyestuffs industry has devoted a considerable amount of research to devising improved methods for the preparation of chromium complex dyestuffs. Before going on to discuss these, however, it is worth considering the preparation of chromium complex dyestuffs from tridentate azo compounds and aquated chromium salts in more detail.

(a) Syntheses employing aquated chromium salts. Typically, the metal-free azo compound is treated with an excess of a chromium(III) salt such as the acetate, chloride or sulfate in aqueous medium at the boil, or at higher temperature under pressure. In the case of azo compounds devoid of sulfonic acid groups it is common to add organic solvents such as alcohol, ethylene glycol or formamide to overcome solubility problems. Increasing acidity of the reaction mixture favours the formation of 1:1 chromium complexes and at a pH of 1.9 or below the 1:1 complex is usually the sole product. At higher pH values of the order of 7 or above the 2:1 chromium complex is usually obtained. The use of a particular chromium salt is, therefore, determined by the product required. Thus chromium(III) salts of strong acids, such as the chloride or sulfate, which allow the pH of the reaction mixture to fall to low values, are usually employed in the preparation of 1:1 chromium complex dyestuffs. Chromium salts of weak acids, such as the acetate or formate, which exert a marked buffering effect, are used in the preparation of 2:1 complexes.

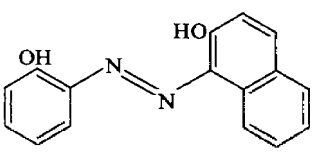
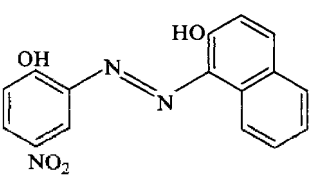
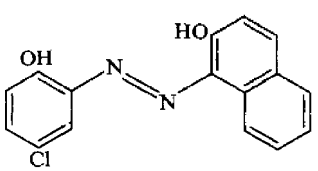
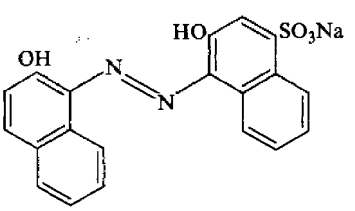
$$DH_2 + [Cr(H_2O)_6]^{3+}3X^- \longrightarrow [DCr(H_2O)_3]^+X^- + 2HX + 3H_2O \quad (1)$$

$$2DH_2 + [Cr(H_2O)_6]^{3+}3X^- \longrightarrow [D_2Cr]^-H^+ + 3HX + 6H_2O \quad (2)$$

$$DH_2 + [DCr(H_2O)_3]^+X^- \longrightarrow [D_2Cr]^-H^+ + HX + 3H_2O \quad (3)$$

DH_2 = tridentate diarylazo compound

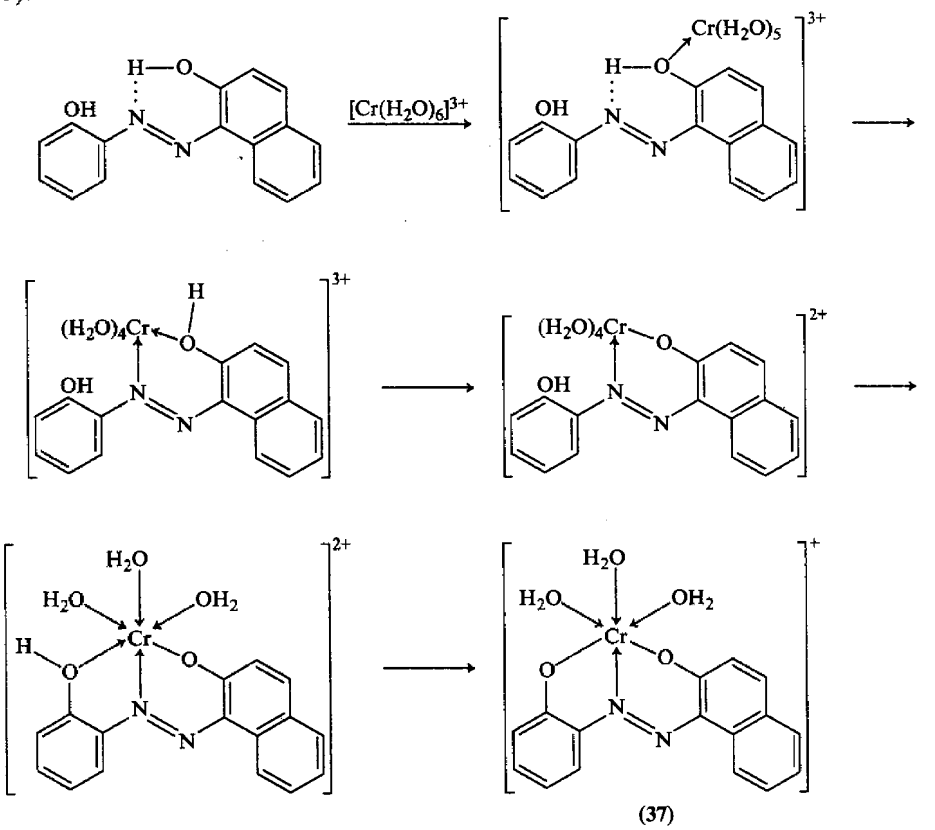
Table 1 pK_a^1 Values of *o,o*-Dihydroxydiarylazo Compounds

Azo compound	pK_a^1	*Azo compound*	pK_a^1
	10.80		7.66
	10.20		9.66

In simple terms the overall reactions involved in the formation of the 1:1 and 2:1 chromium complexes may be represented by equations (1) and (2) respectively. In fact the formation of the 2:1 chromium complex must involve the intermediacy of the 1:1 chromium complex (equation 3). It is, therefore, significant that when the reaction between a tridentate azo compound and a chromium salt is carried out under conditions which result in the formation of the 2:1 chromium complex, *i.e.* at relatively high pH, no 1:1 complex is detected in the reaction mixture. The obvious conclusion to be drawn from this is that the second reaction (equation 3) occurs very much more rapidly than does the first (equation 1) and that the rate-determining step is involved in the formation of the 1:1 complex. Further, the overall reaction is very much more rapid at high than

at low pH values and, indeed, this has been utilized in the preparation of 1:1 chromium complexes. The metallizable azo compound is first converted to its 2:1 chromium complex at relatively high pH and the latter is treated with a mineral acid to obtain the 1:1 complex. In the light of the reported[29] pK_A^1 values of a series of *o,o'*-dihydroxydiarylazo compounds (Table 1), the clear implication of this is that the hexaaquachromium ion reacts more rapidly with the ionized azo compound than with the un-ionized form. However, it is equally apparent that the hexaaquachromium ion can react with the latter to form a complex in which deprotonation of the ligand has occurred.

Unfortunately, although several authors[30] have studied the kinetics of the overall reaction, no conclusive results have been obtained since the system is not really suitable for study by the usual titration methods because of the very slow rate of reaction.[31] It is, however, possible to make reasonable speculations regarding the rate-determining step on the basis of the reported results (Scheme 3).



Scheme 3

The first step in the formation of a 1:1 chromium complex by the interaction of an *o,o*-dihydroxydiarylazo compound and the hexaaquachromium ion at low pH must involve replacement of a coordinated water molecule in the hexaaquachromium(III) ion by one of the donor atoms in the azo compound. The next step in the reaction sequence is formation of a chelate complex by replacement of a further molecule of coordinated water. Polarization of the ligand as a result of chelate formation markedly enhances its acidity and proton loss ensues (*cf.* Section 58.2.2.1).

Replacement of a further coordinated water molecule by the remaining phenolic oxygen atom in the azo compound gives a complex in which the metal atom is a member of two annelated chelate rings. Proton loss from the chelated azo compound, again promoted by the polarization associated with coordination to the positively charged metal ion, then leads to the 1:1 chromium complex (**37**).

Thus five steps are involved in the reaction between a hexaaquachromium(III) ion and an *o,o'*-dihydroxydiarylazo compound at low pH to form the 1:1 chromium complex dyestuff: three ligand replacement reactions and two ionization stages. Studies with other ligands lead to the conclusion that the probable rate-determining step is replacement of the first of the six coordinated water molecules in the highly symmetrical hexaaquachromium(III) ion by one of the donor functions of the ligand. For example, it has been shown[32] that the rate of reaction between the hexaaquachromium(III) ion and the bidentate oxalate or malonate ions to form monochelate

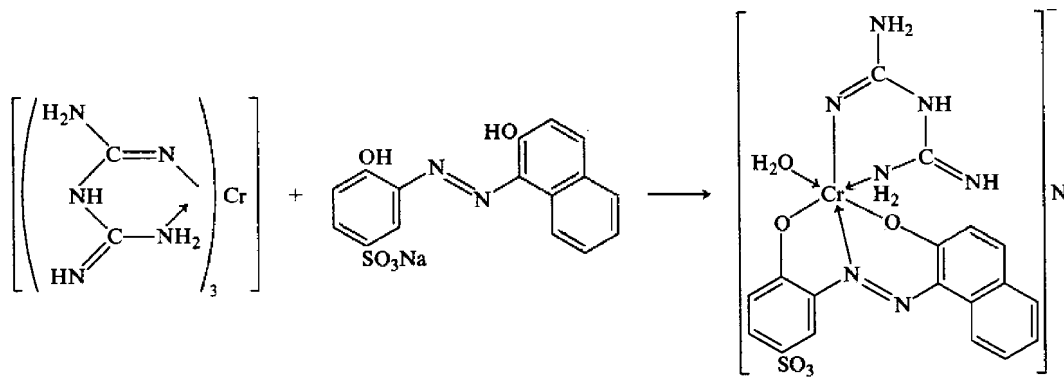
complexes (equation 4), although slow, is effectively the same as that between the hexaaquachromium(III) ion and acetate ions to form the monoacetate complex (equation 5), *i.e.* the second, chelation step is relatively fast. Similarly, it has been reported[33] that the first step in the reaction between the hexaaquachromium(III) ion and glycine to form a chelate complex is slow and determines the overall rate.

$$[Cr(H_2O)_6]^{3+} + {}^{-}OCOCO_2^{-} \xrightarrow{\text{slow}} [(H_2O)_5CrOCOCO_2^{-}]^{+} \xrightarrow{\text{fast}} \left[(H_2O)_4Cr\begin{smallmatrix}O\text{-}CO\\ |\\ O\text{-}CO\end{smallmatrix}\right]^{+} \quad (4)$$

$$[Cr(H_2O)_6]^{3+} + MeCO_2^{-} \xrightarrow{\text{slow}} [(H_2O)_5CrOCOMe]^{2+} \quad (5)$$

In considering improved methods for the manufacture of chromium complexes of tridentate, metallizable azo compounds it is therefore necessary to examine means by which the first step can be accelerated. It is known that the conjugate base of the highly symmetrical hexaaquachromium ion undergoes ligand exchange reactions much more readily than the latter as a result of the labilizing effect of the coordinated hydroxo group.[34] The hexaaquachromium(III) ion is a relatively strong acid,[35] pK_a 3.8, and the reaction between chromium salts and *o,o'*-dihydroxydiarylazo compounds should, therefore, proceed more rapidly at high than at low pH values. This should also be assisted by the increased nucleophilicity of the ligand as a result of its dissociation under these conditions. This is borne out by practical experience but reaction is still slow and is complicated by the formation of hydroxo-bridged or 'olated' and oxo-bridged or 'oxolated' chromium species,[36] leading ultimately to precipitation of chromium hydroxide. Further, under these conditions the product is the symmetrical 2:1 chromium complex of the azo compound. Whilst symmetrical 2:1 chromium complexes still enjoy an important place in the dyestuffs field, for many applications they have been superseded technically by unsymmetrical 2:1 chromium complexes, which are manufactured by the interaction of the 1:1 chromium complex of one tridentate azo compound and an equimolecular amount of a different metal-free tridentate azo compound, *e.g.* that in (**10**). The efforts of the dyestuffs industry to devise improved methods for the manufacture of chromium complex dyestuffs have, therefore, been directed towards the preparation of both 2:1 and 1:1 chromium complexes and one approach has been to use less stable species than the hexaaquachromium(III) ion as a source of metal in the chroming reaction.

(b) Syntheses employing complex chromium(III) compounds. This approach has achieved considerable practical success and hexaureachromium(III) chloride[37] has been shown[38] to react very rapidly with *o,o'*-dihydroxydiarylazo compounds in aqueous medium at pH 7 and 65 °C to give the 2:1 chromium complex of the azo compound. No excess of hexaureachromium(III) chloride is required and the reaction proceeds to completion within minutes.



(**38**) (**39**)

In an alternative approach, designed to overcome the problems of olation and oxolation associated with the use of hexaaquachromium(III) salts in aqueous medium at high pH, anionic chromium complexes have been employed. These include oxalato,[39] tartrato[40] and salicylato[41] complexes. They are reported to react rapidly with *o,o'*-dihydroxydiarylazo compounds in aqueous medium at high pH, usually to give the 2:1 chromium complex of the azo compound. In certain cases, however, 1:1 complexes are obtained in which the coordination sphere of the chromium is at least partially completed by the organic ligand, *e.g.* salicylic acid.[42] In a modification,[43] an alkaline solution of the tridentate azo compound is treated with the complex chromium compounds formed by the interaction of alkaline suspensions of chromium hydroxide and organic polyhydroxy

compounds such as glycerol. The structures of the chroming agents have not been determined but the use of the glycerol complex is claimed to eliminate the need to use excess chromium since the reaction proceeds quantitatively to give the 2:1 chromium complex of the azo compound.

So far as the very important 1:1 chromium complexes are concerned, the introduction[44] of tris(biguanidato)chromium(III) (**38**) as a chroming agent represented a very significant step forward. This compound is soluble in water and reacts rapidly with *o,o'*-dihydroxydiarylazo compounds at temperatures of the order of 60 °C to give 1:1 chromium complex dyestuffs (**39**) in which the coordination sphere of the chromium is at least partially completed by a biguanide molecule. These react readily with a further molecule of the same azo dyestuff to give the symmetrical 2:1 complex, or with an equimolar quantity of a different tridentate metallizable azo compound to give the commercially very important unsymmetrical 2:1 chromium complexes.

(ii) Cobalt complexes

Like d^3 chromium(III) complexes, d^6 cobalt(III) complexes are kinetically inert (Section 58.2.3.1(ii)) and ligand replacement reactions are slow. However, although corresponding chromium(III) and cobalt(III) complexes are frequently very similar in behaviour, the standard methods employed in their preparation are often quite different.[45] The principal reason for this is the very large difference in the redox properties of the hexaaquachromium(III) and the hexaaquacobalt(III) ions. The latter is a powerful oxidizing agent and attacks many organic compounds, whereas the hexaaquachromium(II) ion is a strong reducing agent. Consequently cobalt(III) complexes are usually prepared by oxidation of the appropriate cobalt(II) complex. Thus 2:1 cobalt(III) complexes of tridentate metallizable azo compounds are normally prepared by the interaction of the ligand and a cobalt(II) salt in aqueous medium at relatively high pH. Unless the reaction is carried out with extreme care at very high pH,[46] the product is invariably the diamagnetic 2:1 cobalt(III) complex rather than the 2:1 cobalt(II) complex. The change in oxidation state of the metal ion occurs at the expense of the azo compound, some of which is reduced,[47] and the addition of various oxidizing agents, such as nitrobenzene-4-sulfonic acid, has been recommended[46] to overcome this problem.

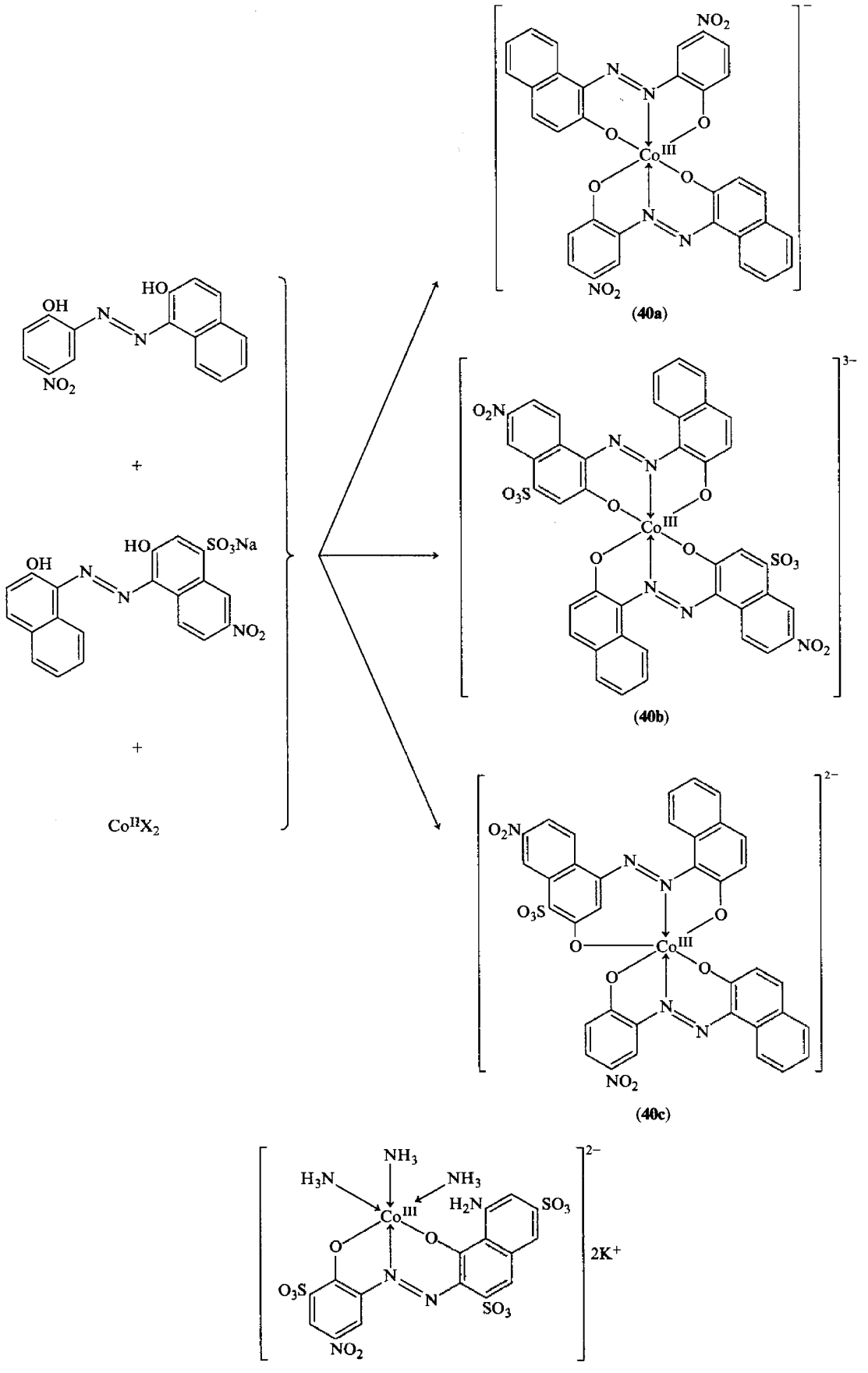
Cobalt complexes of tridentate metallizable azo compounds do not occupy such an important position in the dyestuffs field as chromium complexes. Without doubt the principal reason for this is the fact that 1:1 cobalt complexes cannot be prepared by methods analogous to those employed in the preparation of 1:1 chromium complexes (Section 58.2.3.1(i)). It is, therefore, impossible to prepare unsymmetrical 2:1 cobalt(III) complex dyestuffs by methods comparable to those used in the preparation of unsymmetrical 2:1 chromium complexes. So-called unsymmetrical 2:1 cobalt complexes have been prepared[48] by the interaction of cobalt(II) salts and equimolecular mixtures of two different metallizable azo dyestuffs but these are, in fact, statistical mixtures of the three possible 2:1 complexes (**40a–c**).

It was not until 1965 that 1:1 cobalt(III) complexes of tridentate azo compounds were prepared[49] by the interaction of the azo compound and a cobalt(II) salt in aqueous medium in the presence of excess ammonia under an inert atmosphere. In every case, *e.g.* (**41**), the coordination sphere of the cobalt ion was completed by three molecules of coordinated ammonia and oxidation to the cobalt(III) state occurred at the expense of the azo compound, some of which was reduced. The scope of the reaction is wide and 1:1 cobalt(III) complexes of this type have been prepared from a wide range of tridentate metallizable azo compounds.

$$DH_2 + \left[Co^{II}(H_2O)_6\right]^{2+} \longrightarrow \underset{\text{(labile)}}{\left[DCo^{II}(H_2O)_3\right]} \xrightarrow{DH_2} \left[D_2Co^{II}\right]^{2-} \longrightarrow \underset{\text{(inert)}}{\left[D_2Co^{III}\right]^-} \qquad (6)$$

$$\left[DCo^{III}(H_2O)_3\right]$$

The effective cobalting agent in these reactions is presumably[50] a high cobalt(II) ammine although this has not been confirmed experimentally because of the problems associated with these complexes, their oxidation potentials being such that atmospheric oxygen readily effects their conversion to the kinetically inert cobalt(III) state. The difference in the behaviour of tridentate azo compounds in their reactions with aquated cobalt(II) salts on the one hand and cobalt(II) ammines on the other has been attributed[19] to differences in the oxidation potentials of the respective 1:1 cobalt(II) complexes. In the former case this is such that oxidation to the kinetically inert 1:1 cobalt(III) complex does not occur under the conditions of the reaction and the kinetically labile 1:1 cobalt(II) complex undergoes further ligand exchanges to give the 2:1 cobalt(II) complex.



(40a)

(40b)

(40c)

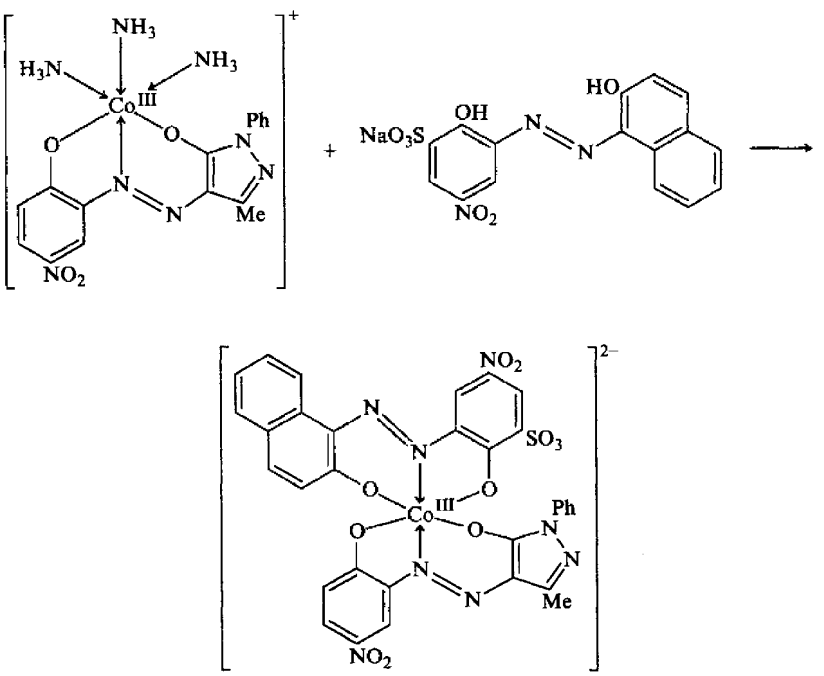
(41)

Its oxidation potential is such that it is oxidized to the kinetically inert 2:1 cobalt(III) complex (equation 6). The relevant redox potentials have not been measured, but support is provided by the isolation by Wittwer[46] of 2:1 cobalt(II) complexes of tridentate azo compounds. These are stable under only a very limited range of conditions and readily undergo oxidation to the corresponding 2:1 cobalt(III) complexes.

In contrast, the oxidation potential of the 1:1 cobalt(II) complex dyestuff in which the coordination sphere of the metal is completed by three molecules of ammonia is such that oxidation to the kinetically inert 1:1 cobalt(III) complex occurs rapidly (equation 6a).

$$DH_2 + [Co^{II}(NH_3)_6]^{2+} \longrightarrow [DCo^{II}(NH_3)_3] \rightarrowtail [D_2Co^{II}]^{2-}$$
$$\downarrow$$
$$[DCo^{III}(NH_3)_3]^{+} \quad \text{(inert)} \qquad (6a)$$

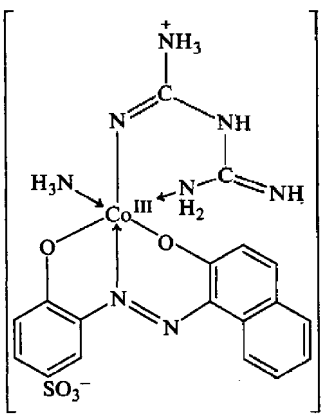
The stability of 1:1 cobalt complex dyestuffs of this type varies considerably according to the nature of the metallizable system in the azo compound. For example, neutral aqueous solutions of 1:1 cobalt complexes of *o*-hydroxyarylazopyrazolones are stable almost indefinitely at 60 °C. Under similar conditions, 1:1 cobalt complexes of *o*,*o*′-dihydroxydiarylazo compounds slowly decompose with loss of ammonia to give the symmetrical 2:1 cobalt(III) complex of the azo compound. The corresponding complexes of *o*-carboxy-*o*′-hydroxydiarylazo compounds decompose rather more rapidly at 60 °C, and those of *o*-carboxyarylazopyrazolones are unstable in aqueous solution at room temperature in the absence of excess ammonia. None is sufficiently stable to be of value as a dyestuff in its own right but the isolation of complexes of this type opened the way to the production[51] of pure, unsymmetrical 2:1 cobalt(III) complex dyestuffs for the first time (*e.g.* **42**). 1:1 Cobalt complex dyestuffs have also been prepared by the interaction of tridentate metallizable azo compounds and cobalt(II) salts in the presence of inorganic nitrites. These too are reported[52] to react with an equimolar quantity of a different tridentate metallizable azo compound to yield a pure unsymmetrical 2:1 cobalt(III) complex.



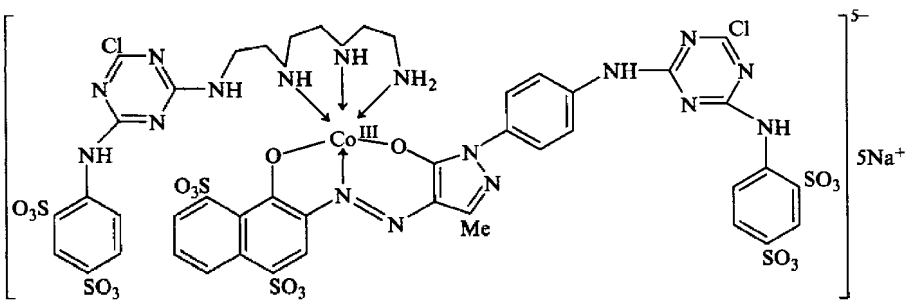
(42)

In general, 1:1 cobalt(III) complex dyestuffs are considerably brighter in hue than the comparable symmetrical 2:1 cobalt(III) complexes and in an endeavour to prepare more stable variants of the former this work was extended to bidentate and tridentate nitrogen-donor ligands. 1:1 Cobalt(III) complex dyestuffs containing coordinated bidentate ligands such as ethylenediamine, 1,3-diaminopropane, 2,2′-bipyridyl, 1,10-phenanthroline and biguanide were prepared by various methods. Reaction of the tridentate azo compound with the cobalt(III) complex of the bidentate ligand was effective in some cases but was restricted in scope since certain complexes, such as tris(biguanidato)cobalt(III), are insufficiently soluble in water. Other complexes, such as tris-

(ethylenediamine)cobalt(III) chloride, frequently formed insoluble dyestuff salts of the complex cation. Reaction of the 1:1 cobalt(III) complex dyestuff containing coordinated ammonia with the free bidentate ligand, however, was reported[53] to afford a general method for the preparation of 1:1 cobalt(III) complex dyestuffs containing coordinated bidentate, nitrogen-donor ligands. These, *e.g.* (**43**), are considerably more stable than the comparable complexes containing monodentate ligands and cannot be used for the preparation of unsymmetrical 2:1 cobalt(III) complex dyestuffs. Even more stable are 1:1 cobalt(III) complex dyestuffs in which the coordination sphere of the metal is completed by a tridentate nitrogen-donor ligand[53–55] such as terpyridyl or diethylenetriamine. These, which are reported[53] to be best prepared by the interaction of a tridentate, metallizable azo compound and, for example, bis(diethylenetriamine)cobalt(III) chloride, are stable and show no sign of degradation or disproportionation in boiling aqueous solution. By varying the degree of sulfonation of the azo compound the net charge on the 1:1 cobalt(III) complex dyestuff can range from +1 (suitable for acrylic fibres), through 0 (pigments), −1, −2 (suitable for wool) to multiple-negatively charged types which, in the form of their fibre-reactive derivatives, are suitable for cellulosic fibres. An interesting variation on the latter involves attaching the fibre-reactive group to the colourless nitrogen-donor ligand. Thus the dyestuff (**44**) is reported[50] to give moderately bright red shades on cotton and has excellent fastness properties, particularly to light.



(**43**)



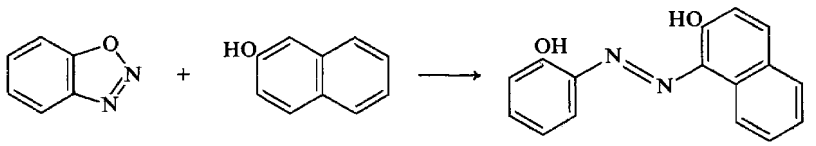
(**44**)

(iii) Copper complexes

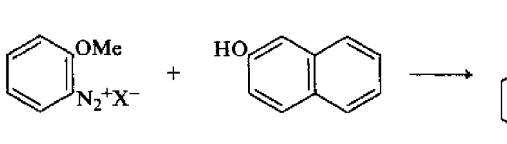
The preparation of copper complexes of tridentate, metallizable azo compounds presents few difficulties and is usually carried out by reaction with a copper salt in aqueous medium at temperatures of the order of 60 °C. However, certain other methods of preparation are of considerable technological as well as theoretical interest. These are often employed in cases where the preparation of the parent azo compound is itself difficult.

(a) Demethylative coppering of o-*methoxy*-o′-*hydroxydiarylazo compounds.* o,o′-Dihydroxydiarylazo compounds are normally prepared by the interaction of a diazotized *o*-aminophenol or naphthol and a phenol or a naphthol (equation 7). In some cases, however, this reaction does not proceed well and low yields of impure products are produced. One method of overcoming this problem is to employ the more reactive diazonium compound derived from the corresponding *o*-aminoanisole (equation 8). The resulting *o*-alkoxy-*o*′-hydroxydiarylazo compound is then converted to the copper complex of the corresponding *o*,*o*′-dihydroxydiarylazo compound by reaction with a copper salt, typically the sulfate, in the presence of ammonia and, frequently, an alkanolamine in aqueous medium at elevated temperature (equation 9). This dramatically facilitated

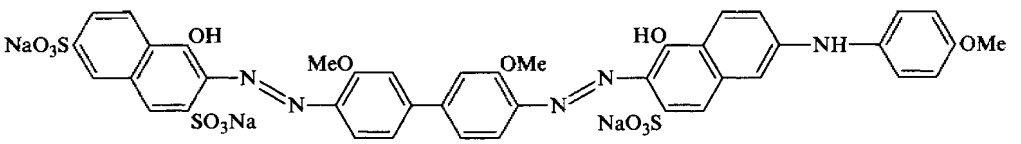
dealkylation of an alkyl aryl ether is a good example of modification of the properties of a ligand on coordination.



(7)

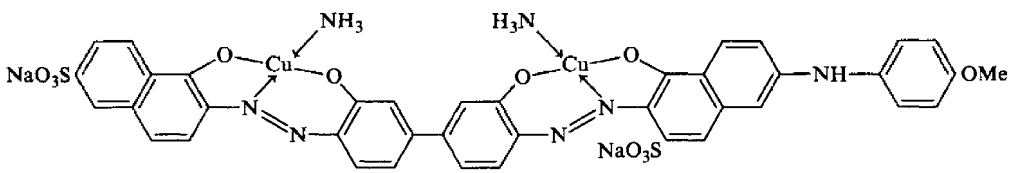


(8)

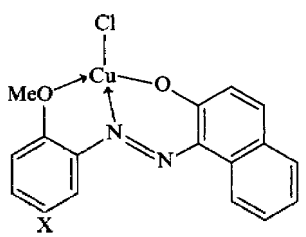




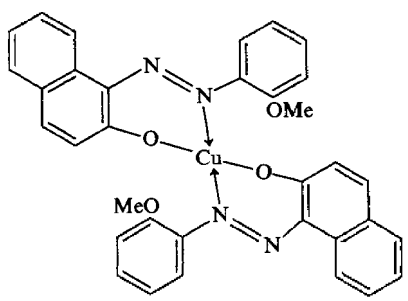
(9)



1-(2-Methoxyphenylazo)-2-naphthol reacts with copper(II) chloride in ethanol to give a complex having 1:1 stoichiometry[56] which has been formulated as (**45**; X = H). This complex readily undergoes demethylation under very mild conditions in aqueous pyridine or ammonia to give the copper complex of 1-(2-hydroxyphenylazo)-2-naphthol. In contrast, the 2:1 copper complex of 1-(2-methoxyphenylazo)-2-naphthol (**46**) undergoes the corresponding reaction only very slowly under similar conditions, leading to the conclusion that coordination of the methoxy group to the metal is necessary for facile dealkylation to occur.



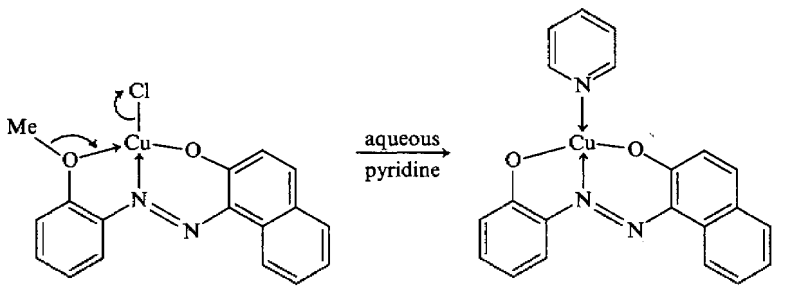
(**45**)



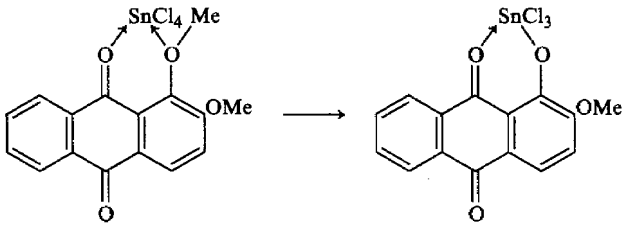
(**46**)

Mur[56] has shown that the rate of dealkylation of complexes such as (**45**) is influenced by substituents *para* to the methoxy group, the descending order of effect on rate being X = NO_2 > H > MeO > Me > Cl. This could be taken to imply nucleophilic attack by hydroxyl ion at the carbon atom attached to the methoxy group. However, in contrast to coppering reactions involving nucleophilic replacement of a halogen atom *ortho* to the azo group (Section 58.2.3.1(iii)(c)), the methoxy group cannot be replaced by nucleophiles such as ammonia or amines. It is, therefore, reasonable that the methyl group is lost as a carbon cation, this being assisted by coordination of the methoxy group (equation 10). A direct analogy is the selective dealkylation of 1,2-dimethoxyanthraquinone in the presence of tin(IV) chloride (equation 11).[57]

(b) Oxidative coppering of o*-hydroxydiarylazo compounds.* As in demethylative coppering, this method, reviewed by Pfitzner and Baumann,[58] also finds application in the preparation of copper complexes of *o,o'*-dihydroxydiarylazo compounds which are themselves difficult to prepare. In general, diazonium compounds derived from aromatic amines with no hydroxy group *ortho* to the amino group are very much more reactive than those with one. Consequently, in some cases it is very much easier and more economical to prepare an *o*-hydroxydiarylazo compound than the



(10)

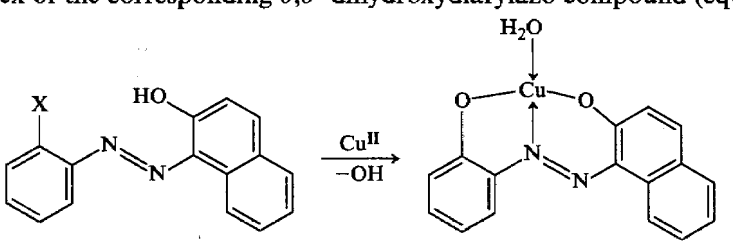


(11)

corresponding *o,o'*-dihydroxydiarylazo compound. The *o*-hydroxydiarylazo compound is then converted to the copper complex of the corresponding *o,o'*-dihydroxydiarylazo compound with an oxidizing agent in the presence of a copper salt. Most commonly used is hydrogen peroxide, but salts of peroxy acids have also been employed. The reaction is usually carried out in aqueous medium at 40–70 °C and at pH 4.5–7.0. This is a further example of how the reactivity of ligands is markedly altered when they become coordinated. In the absence of copper(II) ions, treatment of an *o*-hydroxydiarylazo compound with hydrogen peroxide results in a gross mixture of variously oxidized species.

Some information regarding the mechanism of the oxidative coppering reaction has been provided by Idelson *et al.*[59] and Yoshida and his coworkers.[60] Both sets of workers consider that the reaction proceeds through the 1:1 copper(II) complex of the *o*-hydroxydiarylazo compound although neither succeeded in isolating such a species. Solutions containing the azo compound and an excess of copper(II) acetate were treated with hydrogen peroxide to obtain the desired product. The formation of a 1:1 copper complex of the *o*-hydroxydiarylazo compound under these conditions appears unlikely since even in the presence of a large excess of copper(II) acetate such compounds react with the latter reagent to form 2:1 complexes. However, the use of an equimolecular amount of a copper(II) salt is necessary for the formation of the 1:1 copper complex of the *o,o'*-dihydroxydiarylazo compound, which is the product of the reaction. It appears probable[61] that the copper ion functions as a 'template' in this reaction, localizing oxidative attack on the *o*-hydroxydiarylazo compound to the *o'*-position.

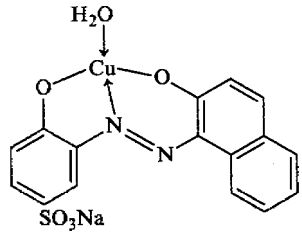
(c) Preparation from o-*halogeno*-o'-*hydroxydiarylazo compounds.* As in the two previous sections, the principal application of this method is in the syntheses of copper complexes of *o,o'*-dihydroxydiarylazo compounds which are themselves difficult to prepare. In practice, an *o*-halogeno-*o'*-hydroxydiarylazo compound is treated with a copper salt in alkaline medium to obtain the complex of the corresponding *o,o'*-dihydroxydiarylazo compound (equation 12).



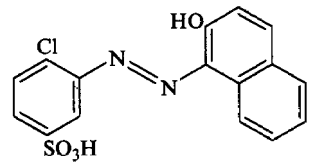
(12)

X = Cl, Br, I

The most interesting feature of this method, reviewed by Stepanov,[62] is the ease with which the halogen atom is replaced by a hydroxyl group during the metallization process. This was first observed as long ago as 1931 when Delfs[63] obtained the copper complex of 2-(2-hydroxynaphthyl-1-azo)phenol-4-sulfonic acid (**47**) by heating an aqueous solution of 1-chloro-2-(2-hydroxynaphthyl-1-azo)benzene-4-sulfonic acid (**48**), copper sulfate, sodium hydroxide and ammonia at 80 °C for 1 hour.

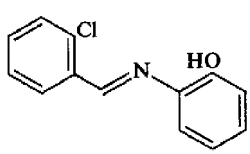


(47)

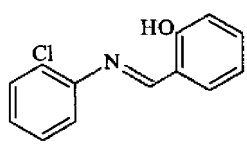


(48)

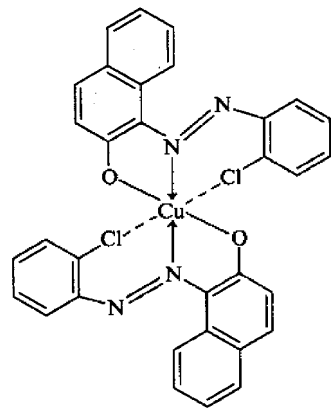
The nucleophilic replacement of halogen atoms in aromatic compounds proceeds under mild conditions only if the halogen atom is strongly activated by suitably located electronegative substituents. The activating effect of the azo group is low,[64] but in the presence of copper salts *o*-halogeno substituents can be replaced[65] by a variety of nucleophiles, including alkoxide, phenoxide, β-dicarbonyl, sulfinate, cyanide, nitrite and dialkyl phosphite ions, ammonia, aliphatic and aromatic amines, and trialkyl phosphites, under mild conditions. It is noteworthy that halogen atoms in a position *para* to an azo group do not undergo similar nucleophilic substitution reactions under corresponding conditions. It is tempting, therefore, to invoke a mechanism based on the formation of a copper chelate complex involving the halogen atom and one of the nitrogen atoms of the azo group to account for the susceptibility of the former to nucleophilic replacement. In this context, Stepanov[66] has shown that whereas the Schiff's base (**49**) reacts with alcoholate ions in the presence of copper ions with replacement of the chlorine atom by an alkoxy group, the isomeric (**50**) fails to react. He proposed that the high mobility of the chlorine atom in *o*-halogenodiarylazo compounds is due to interaction between the chlorine atom and the copper ion in a complex in which the metal is a member of a five-membered chelate ring involving the oxygen atom (**51**).



(49)



(50)

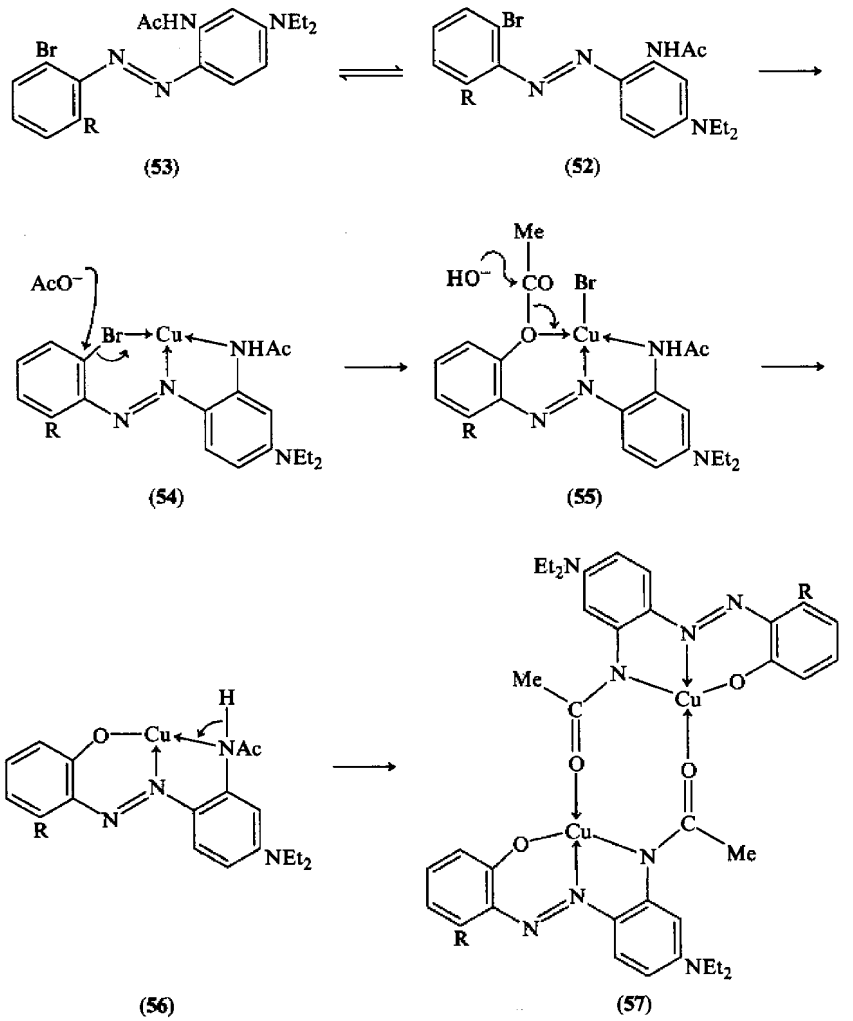


(51)

This appeared unlikely for several reasons: firstly, *o*-hydroxydiarylazo compounds form copper complexes in which the metal atom forms a part of a six-membered chelate ring and, secondly, interaction between the hydrogen atom in the 8-position of the naphthalene nucleus and the lone pair on the β-nitrogen atom of the azo group would not favour a structure such as (**51**).

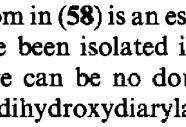
However, more recently Price and Yates[67] have shown that *o*-bromo-*o'*-acetylaminodiarylazo compounds react with acetate ions in the presence of copper(II) acetate in dipolar aprotic solvents under very mild conditions to give the copper(II) complexes of the corresponding *o*-hydroxy-*o'*-acetylaminodiarylazo compounds. From the effect of substituents in the parent bromo compound on rates, they proposed the mechanism in Scheme 4. Enhancement of the reactivity of the *o*-bromodiarylazo compound when R is a group other than hydrogen, irrespective of its polar character, led them to infer that structure (**52**) is more favourable for this reaction than is structure (**53**). This was in firm agreement with earlier, similar observations.[68,69] Nucleophilic attack by carboxylate ion is facilitated by polarization of the carbon–bromine bond resulting from the formation of an annelated copper(II) complex of partial structure (**54**). The intermediate formation of the *o*-acetoxy-*o'*-acetylaminodiarylazo compound (**55**) was demonstrated conclusively. Coordination of the ester group with the copper ion in the complex of partial structure (**55**) considerably enhances the electrophilic character of the acyl carbon atom and consequently hydrolysis of the ester group occurs readily to give the intermediate of partial structure (**56**). Proton loss from the latter leads to the product (**57**) which is interesting on several counts: it is the first recorded example of a metal

complex dyestuff based on the *o*-hydroxy-*o'*-acetylaminodiarylazo system in which the acetylamino group functions as a bidentate donor, and a proton has been lost from the acetylamino group.



Scheme 4

From these and other unpublished results it can be concluded that the halogen in compounds of general structure (**58**) is activated towards nucleophilic attack to a remarkable degree by copper salts. The double bond to the nitrogen atom in (**58**) is an essential feature of its structure and, whilst no copper-containing intermediates have been isolated in copper-promoted nucleophilic substitutions of compounds of this type, there can be no doubt that such species are involved. The preparation of copper complexes of *o,o'*-dihydroxydiarylazo compounds by the copper-promoted replacement of the halogen in *o*-halogeno-*o'*-hydroxydiarylazo compounds by a hydroxyl group represents a further example of the industrial exploitation of the modification of the reactivity of ligands coordinated to metal ions.



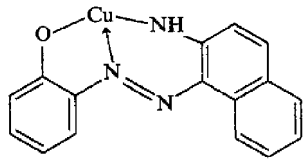
(**58**) X = halogen

58.2.3.2 Tridentate diarylazo compounds containing o*-amino substituents*

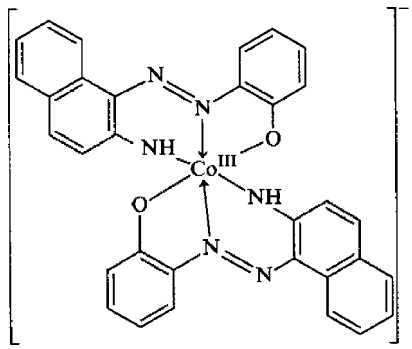
When a ligand becomes coordinated its properties are markedly changed; one example already encountered (Sections 58.2.2.1 and 58.2.3.1(i)(a)) is the enhancement of the acidity of the phenolic hydroxyl groups in *o*-hydroxydiarylazo compounds coordinated to metal ions. *o*-Aminodiarylazo compounds apparently offer an even more dramatic example.

The ability of *o*-amino-*o'*-hydroxydiarylazo compounds to react with transition metal salts to form complexes in which two protons are lost from the ligand was first observed[70] with the formation of the copper complex of 1-(2-hydroxyphenylazo)-2-naphthylamine. Analytical results

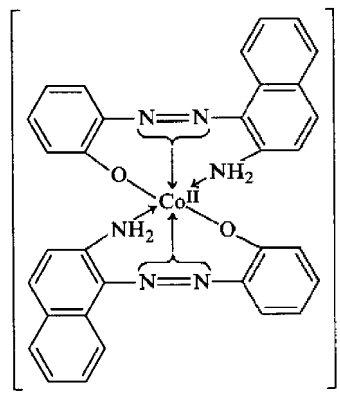
were in good agreement with the formulation (**59**) and it is reasonable to suppose that the coordination sphere of the copper is completed by bridging through the oxygen atoms in a dimeric species. Subsequently, 2:1 cobalt complexes of *o*-hydroxy-*o'*-aminodiarylazo compounds were prepared and formulated as (**60**) by some authors,[71] but as (**61**) by others.[72] More recent work has shown the former structure to be correct. In this work Schetty[73] studied the reaction of the series of *o*-amino-*o'*-hydroxydiarylazo compounds (**62a–e**) with cobalt(II) and cobalt(III) salts.



(**59**)

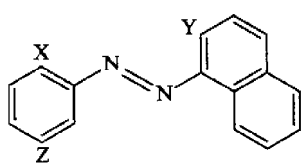


(**60**)



(**61**)

With the sole exception of (**62b**), which reacted with cobalt(II) acetate to give a 2:1 cobalt(II) complex, the product in every case was a 2:1 cobalt(III) complex irrespective of whether the azo compound reacted with a cobalt(II) or a cobalt(III) salt (see Section 58.2.3.1(ii)). The products, however, varied considerably with regard to the number of protons lost from the ligand on complex formation. Thus (**62a**) and (**62b**) gave positively charged 2:1 cobalt(III) complexes $[(LH)_2Co^{III}]^+$, in which only one proton was lost from each ligand. Both (**62c**) and (**62e**) gave mixtures of neutral, $[(LH)LCo^{III}]^0$, and negatively charged, $[L_2Co^{III}]^-$, complexes, whilst (**62d**) gave only a negatively charged, $[L_2Co^{III}]^-$, 2:1 cobalt(III) complex. Measurement of the pK_A values of the various coordinated species was not possible but it is apparent from these results that they follow the sequence (**62d**) < (**62e**) ≈ (**62c**) < $MeCO_2H$ < (**62a**) ≈ (**62b**) with respect to the monodeprotonated ligands. It is also clear that proton loss from the amino group in an *o*-amino-*o'*-hydroxydiarylazo compound occurs very much more readily when the amino group is attached to a naphthalene radical than when it is attached to a benzene radical.

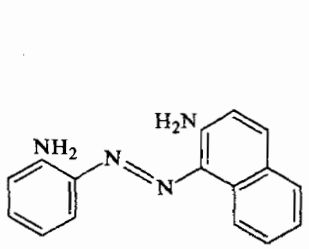


≡ (LH_2)

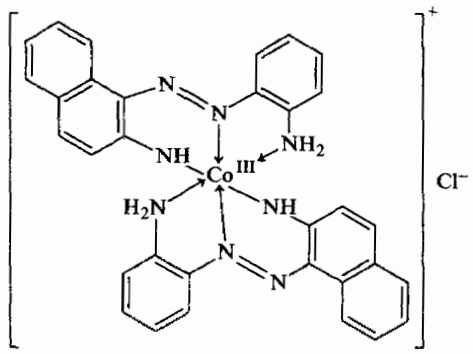
	X	*Y*	*Z*
(**62a**)	NH_2	OH	H
(**62b**)	NHMe	OH	H
(**62c**)	NHMe	OH	SO_2Me
(**62d**)	OH	NH_2	SO_2Me
(**62e**)	OH	NHEt	SO_2Me

A study[74] of cobalt complex formation by a series of related *o,o'*-diaminodiarylazo compounds showed that, in marked contrast to the 1-(2-hydroxyphenylazo)-2-naphthylamine (**62d**), 1-(2-aminophenylazo)-2-naphthylamine (**63**) reacted with cobalt(II) chloride to give a 2:1 cobalt(III) complex (**64**) in which only one proton had been lost from each ligand molecule. This observation led to the proposal that proton loss occurred from the iminohydrazone form of the ligand rather than from a primary amino group.

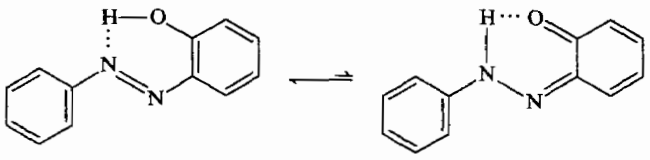
The phenomenon of azo–hydrazone tautomerism is firmly established[75] in the benzeneazophenol, -naphthol, and -anthranol series, the azo form predominating in the first of these (**65**), the hydrazone form in the second (**66**), whilst the third exists exclusively in the hydrazone form (**67**). The situation is less clear in the analogous *o*-aminodiarylazo series. Thus, whilst it is known that *o*-aminoazobenzene (**68**) exists exclusively in the azo form, it has not been established whether



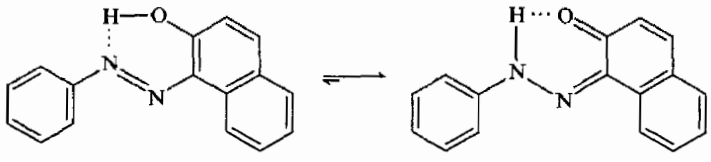
(63)



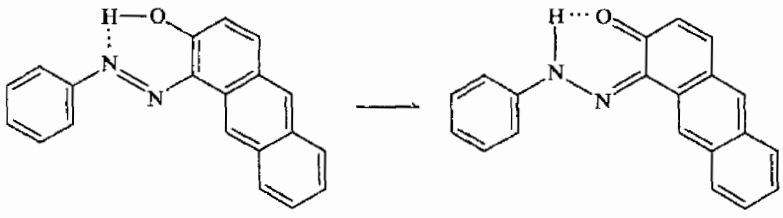
(64)



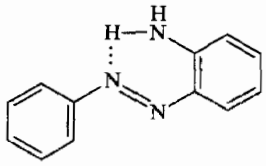
(65)



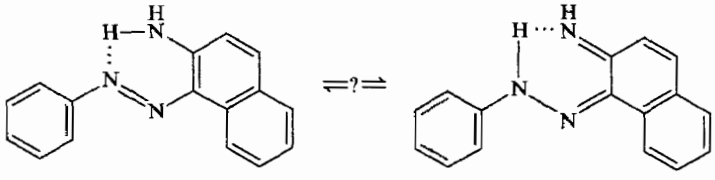
(66)



(67)



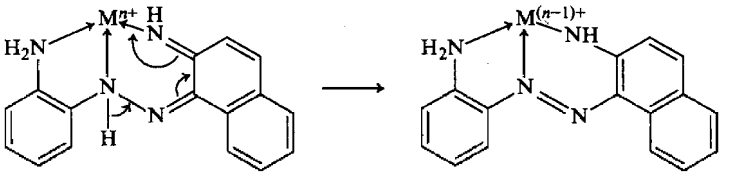
(68)



(69)

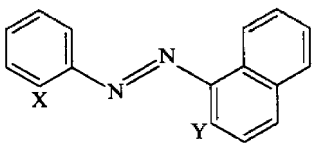
tautomerism exists in 1-phenylazo-2-naphthylamine (**69**), although it has been calculated[4] that the iminohydrazone tautomer is thermodynamically more stable than the azo tautomer. Loss of a proton from the former would be far less surprising than from a primary amino group, since the hydrogen in a hydrazone moiety =C=N—NH—Y tends to be acidic in character, and proton loss would be facilitated by polarization of the hydrazone resulting from coordination to a metal ion (equation 13). Further, if in fact proton loss from an *o*-aminodiarylazo compound does occur from the hydrazone form of the ligand, it follows that only one proton can be lost from an

o,o'-diaminodiarylazo compound on metal complex formation. This is in accordance with the observed[74] results and further support for this hypothesis was provided by the behaviour of other *o,o'*-diaminodiarylazo compounds on reaction with cobalt(II) chloride. This is summarized in Table 2.



(13)

Table 2 Products Obtained by the Interaction of Cobalt(II) Chloride and Various *o,o'*-Diaminodiarylazo Compounds

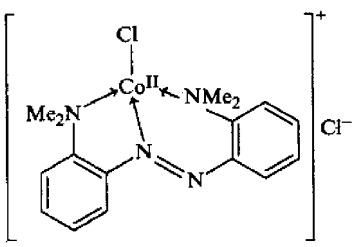


(LH)

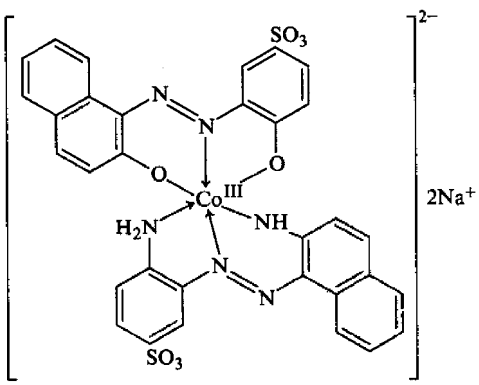
	X	*Y*	*Product*		
(a)	NH_2	NH_2	—	—	$[L_2Co^{III}]^+Cl^-$
(b)	NH_2	NHMe	—	—	$[L_2Co^{III}]^+Cl^-$
(c)	NMe_2	NH_2	—	$[LCo^{II}Cl]$	$[L_2Co^{III}]^+Cl^-$
(d)	NEt_2	NH_2	$[(LH)Co^{II}Cl]^+Cl^-$	$[LCo^{II}Cl]$	—
(e)	NPr^n_2	NH_2	$[(LH)Co^{II}Cl]^+Cl^-$	$[LCo^{II}Cl]$	—
(f)	NMe_2	NHMe	$[(LH)Co^{II}Cl]^+Cl^-$	$[LCo^{II}Cl]$	$[L_2Co^{III}]^+Cl^-$

Three types of cobalt complex were isolated: 1:1 cobalt(II) complexes (**70**) in which no proton loss from the ligand had occurred, 1:1 cobalt(II) complexes (**71**) in which a proton had been lost from the ligand, and 2:1 cobalt(III) complexes (**72**) in which a proton had been lost from both ligand molecules. On the basis of these results, the reaction sequence outlined in Scheme 5 was proposed.

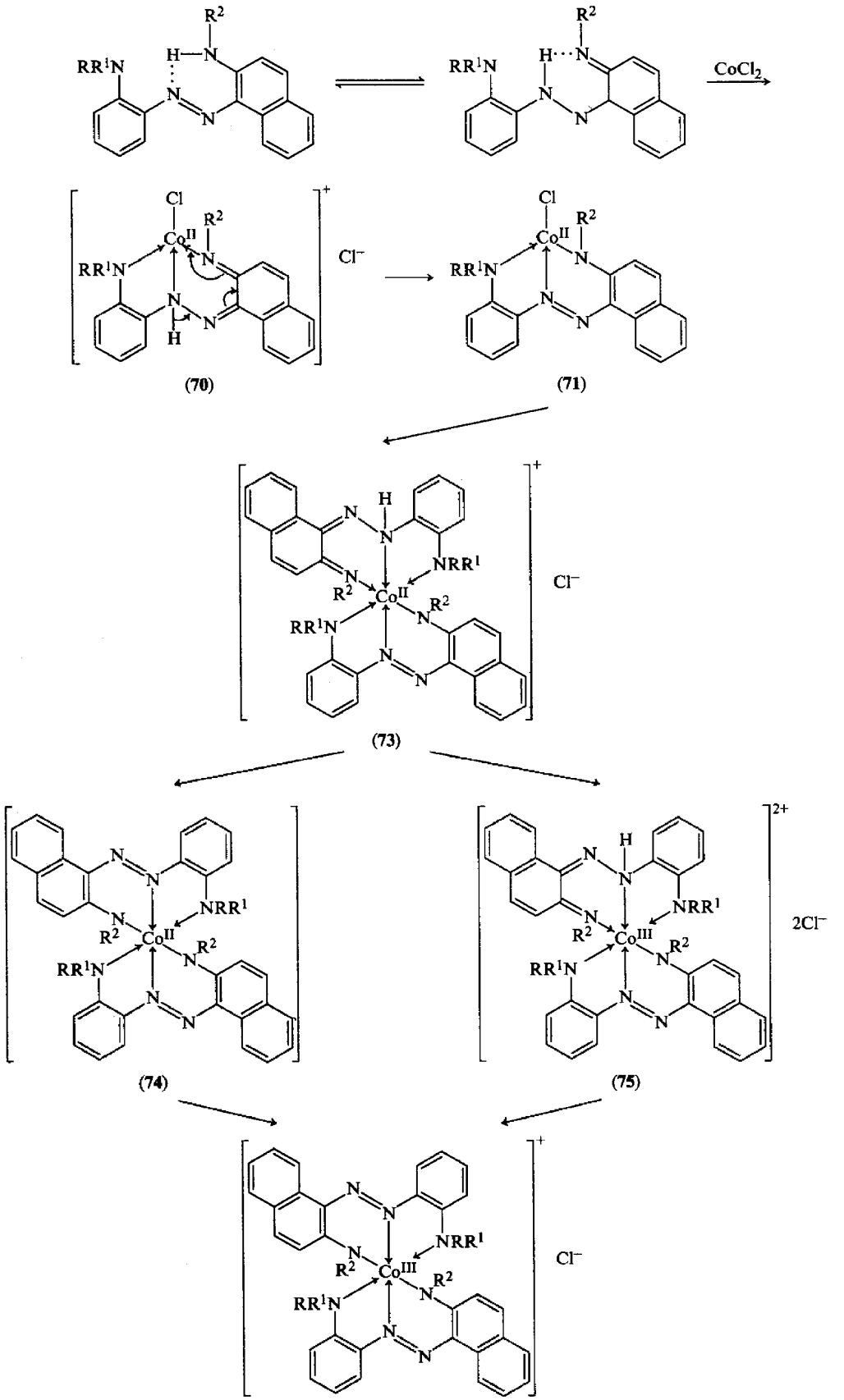
Justification for the formulation of the ligands in the complexes (**70d–f**) in the iminohydrazone form was provided by the different geometry of these complexes (square planar) from that (tetrahedral) of the analogous complex (**76**) in which the ligand cannot attain a hydrazone form. Enhancement of the acidity of the coordinated ligand in complexes of the type (**70**) is related to the strength of the bonds between the ligand and the cobalt ion and, from available evidence[76] on the coordinating ability of substituted amines, this would be anticipated to follow the sequence (**70**; R = R^1 = R^2 = H) > (**70**; R = R^1 = H, R^2 = Me) > (**70**; R = R^1 = Me, R^2 = H) > (**70**; R = R^1 = Et, R^2 = H) > (**70**; R = R^1 = R^2 = Me). 1:1 Cobalt(II) complexes (**70**) were isolated only in the last three cases but their behaviour with regard to deprotonation was in agreement with that expected. The formation of a 2:1 cobalt(III) complex of type (**72**) is visualized as proceeding through a 2:1 cobalt(II) complex (**73**), followed by loss of the elements of hydrogen halide and subsequent oxidation of the resulting complex (**74**) to the cobalt(III) state. Alternatively, oxidation of the 2:1 cobalt(II) complex (**73**) to the cobalt(III) complex (**75**) may precede deprotonation. No experimental evidence is available to distinguish between the two suggested routes since the oxidation potentials of the 2:1 cobalt complexes are such that oxidation to the cobalt(III) state occurs at the expense of the ligand. Consequently no 2:1 cobalt(II) complexes of types (**74**) or (**75**) could be isolated.



(**76**)



(**77**)

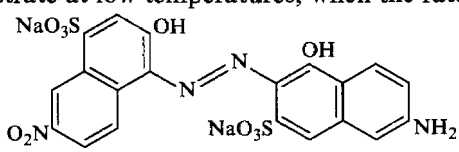


Scheme 5

The fact that only one proton is lost from an *o,o'*-diaminodiarylazo compound on metal complex formation is not only of theoretical interest but has important practical implications in the synthesis of unsymmetrical 2:1 chromium(III) and cobalt(III) complex dyestuffs for wool. The most important complexes of these types are those which are doubly negatively charged (Section 58.1) and are obtained from one molecule of a sulfonated tridentate azo compound and one molecule of an unsulfonated tridentate azo compound. In general the latter are insoluble in water and it is necessary to use organic solvents in the manufacture of complexes such as (**10**). This is very undesirable from the point of view of the dyestuffs manufacturer and any means of avoiding the use of solvents is attractive to him. The use of sulfonated *o,o'*-diaminodiarylazo compounds in combination with, for example, sulfonated *o,o'*-dihydroxydiarylazo compounds opened up one such possibility, *e.g.* (**77**), although this has not yet been exploited commercially.

58.2.3.3 Stereochemistry and isomerism

The isomerism and stereochemistry of metal complexes of tridentate azo compounds have been the subject of numerous investigations over the years because of the perceived relevance of these features to the dyeing and fastness properties of such dyestuffs. The investigations were fuelled when Morris[77] demonstrated that isomeric metal complexes did indeed have markedly different dyeing properties when he succeeded in isolating two isomeric 2:1 chromium complexes of the tridentate 2-amino-6-(2-hydroxy-6-nitro-4-sulfonaphth-1-ylazo)-5-naphthol-7-sulfonic acid (**78**). These were converted into the corresponding fibre-reactive 2-(2,4-dichloro-1,3,5-triazin-6-yl)-amino derivatives and dyed on cotton under very mild conditions. The two isomers showed markedly different cellulose substantivity and this was reflected in their degree of fixation on cotton. Whilst one isomer fixed to the extent of 67%, the other gave only 40% fixation, a very significant difference in performance in technical terms, and the former has obvious attractions to the dyestuffs manufacturer and dyer alike. However, several factors must be considered in assessing the true technological significance of this result. First, the isomers were separated chromatographically from the mixture which was obtained when the azo compound (**78**) was converted into its 2:1 chromium complex. Second, no information is available on the absolute configurations of the two isomeric chromium complexes. Third, and probably most important from the point of view of the dyestuffs chemist and the dyer, the individual isomers reverted very rapidly to their equilibrium mixture in aqueous solution at temperatures of the order of 60 °C. It was for this last reason that Morris converted his products to fibre-reactive derivatives which could be applied to the cellulosic substrate at low temperatures, when the rate of isomerization was slow.

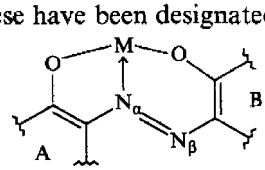


(**78**)

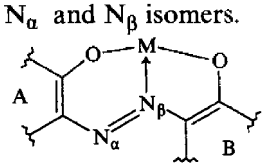
A recurring theme throughout all the reported work on isomerism in metal complexes of tridentate azo compounds is the facility with which individual isomers revert to equilibrium mixtures in solution at elevated temperatures. Since these are the very conditions under which most metal complex dyes are applied, little technical application can be seen for the phenomenon of isomerism on dyes of this type. Nonetheless, the subject is of considerable theoretical interest and merits inclusion in this chapter on those grounds alone.

Isomerism in metal complexes of tridentate azo compounds has been attributed to a number of factors and in the interest of clarity these will first be described in broad terms and then discussed in more detail.

N_α–N_β isomerism: Perhaps the most immediately obvious source of isomerism in metal complexes of tridentate azo compounds is the involvement of different nitrogen atoms of the azo group in coordination to the metal. This is not relevant in the case of symmetrical azo compounds but two structurally isomeric metal complexes (**79**) and (**80**) are conceivable for unsymmetrical azo compounds. These have been designated by Pfitzner[78] as N_α and N_β isomers.

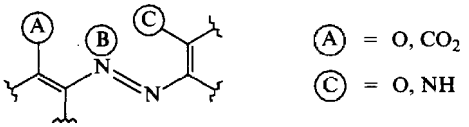


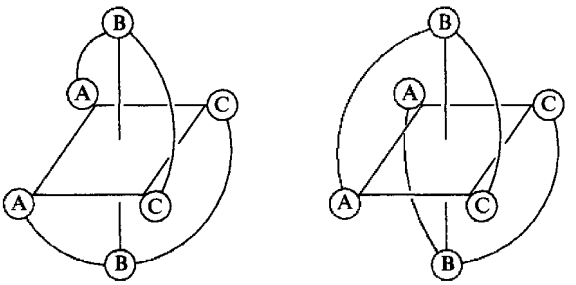
(**79**)



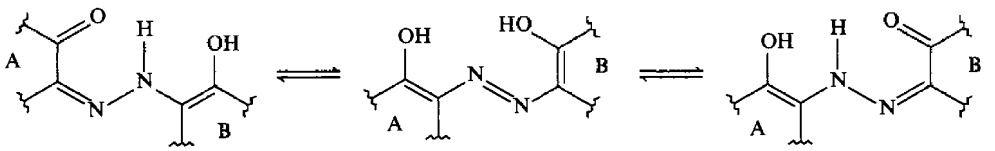
(**80**)

Geometrical isomerism: Geometrical isomerism is possible only in hexacoordinate complexes and in the case of 2:1 metal, *e.g.* chromium and cobalt, complexes arises from coordination of the ligand in a meridional (**81**) or a facial (**82**) mode in an octahedral complex. In the former case only an enantiomorphic pair of isomers is possible, but in the latter the possibility exists of four enantiomorphic pairs and a centrosymmetric isomer (Figure 1).

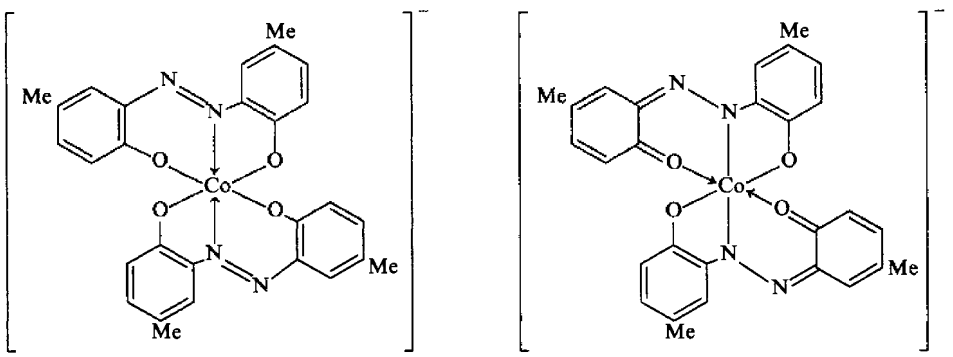


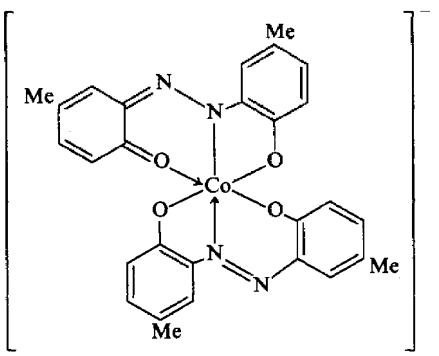


(**81**) (**82**)



(**83**)





(**84**)

Azo–hydrazone tautomerism: Azo–hydrazone tautomerism (**83**) (Section 58.2.3.2) is a well-established phenomenon in *o,o'*-dihydroxydiarylazo compounds, the various species existing in solution as an equilibrium mixture the composition of which is determined by a number of factors including substituents in the azo compound, the nature of the solvent, *etc.* It has been invoked to account for the formation of isomeric 2:1 cobalt(III) complexes by symmetrical *o,o'*-dihydroxydi-

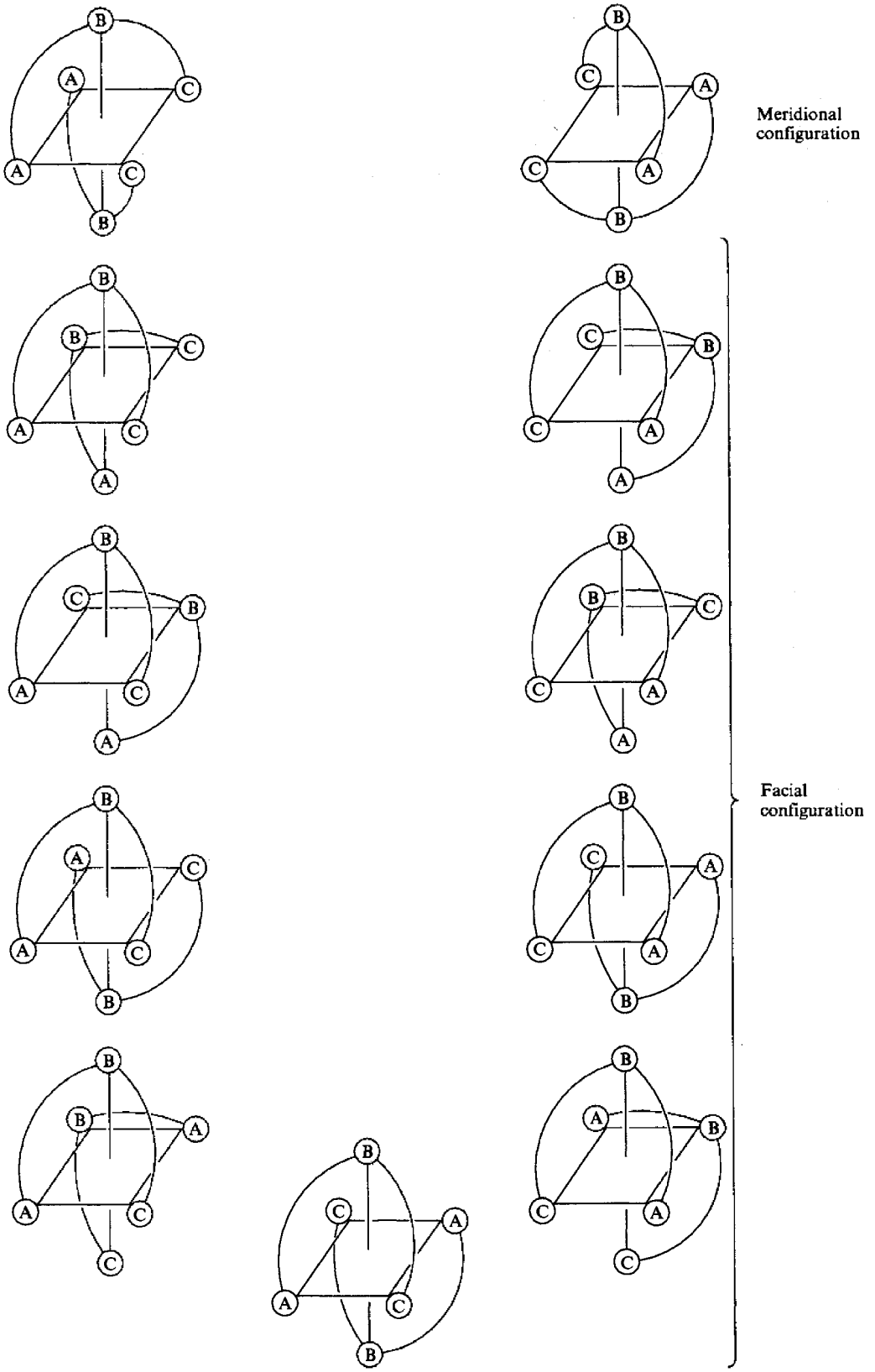
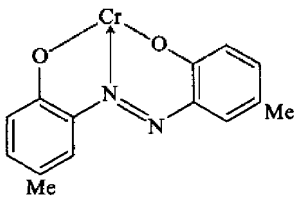


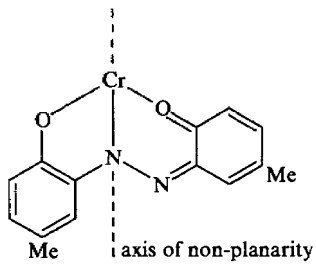
Figure 1 Geometrical isomers of hexacoordinate complexes

arylazo compounds since three possibilities (**84**) appear to exist. The evidence for this particular form of isomerism is somewhat flimsy and is based on the assumption that *o,o'*-dihydroxydiarylazo compounds invariably form meridional complexes.

Isomerism arising from non-planarity in the ligand: The reported isomerism of this type in 2:1 chromium complexes of *o,o'*-dihydroxydiarylazo compounds is also a consequence of azo–hydrazone tautomerism in the latter. When the ligand is coordinated to the chromium ion in the azo form (**85**) the nitrogen donor atom is sp^2 hybridized and planar. In the hydrazone form (**86**), however, the donor nitrogen atom is sp^3 hybridized and, therefore, tetrahedral. This creates a situation in which the ligand can adopt two non-planar configurations and leads to the possibility of three enantiomeric conformers. The evidence for isomerism of this type is open to question and, again, is based on the assumption that *o,o'*-dihydroxydiarylazo compounds invariably form meridional complexes.



(85)

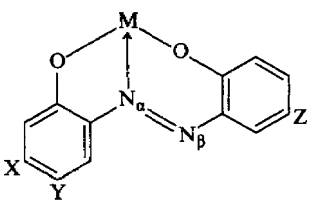


(86)

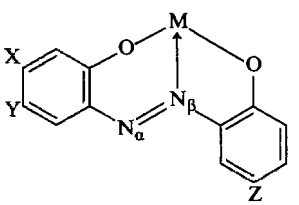
The evidence for the existence of isomeric metal complexes of these various types is, in many cases, largely circumstantial. Further, in some instances conclusions appear to have been drawn on the basis of unwarranted assumptions and alternative explanations for observed phenomena exist. It is felt, therefore, that this topic merits more detailed examination.

(i) N_α–N_β isomerism

(a) Copper and nickel complexes. The formation of copper and nickel complexes of a series of unsymmetrically substituted *o,o'*-dihydroxyazobenzenes has been studied by Pfitzner[78] who showed that in many cases two products were produced. These, which were formed in approximately equal proportions, were separated by chromatography on silica gel using pyridine/benzene as eluant. The products were stated to have the same composition but no analytical details were provided and it must be assumed that the coordination sphere of the metal was completed by pyridine. Since symmetrical *o,o'*-dihydroxyazobenzenes gave only one product (**87**; X = H, Y = Z) under comparable conditions, Pfitzner formulated the products from the unsymmetrical *o,o'*-dihydroxyazobenzenes as the N_α (**87**) and N_β (**88**) isomers, albeit without specifying which was which.



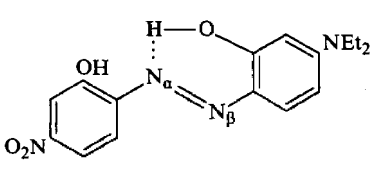
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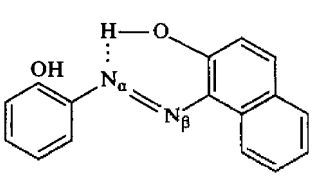
(88)

a; M = Cu
X = Cl, SO_2NH_2
Y = H, Cl, Me, OMe
Z = Cl, Br, Me, OMe, Ph

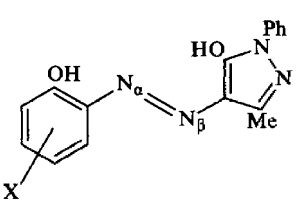
b; M = Ni
X = H, Cl, OMe, NO_2, SO_2NH_2
Y = H, Cl, Me, OMe, NO_2
Z = Cl, Br, Me, OMe, NHAc, Ph



(89)



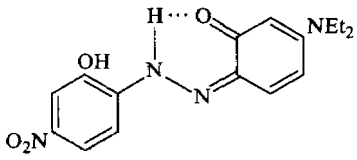
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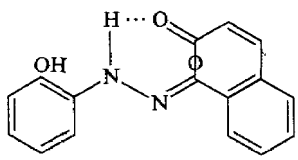
(91)

No isomers were detected in the copper and nickel complexes of the strongly polarized *o,o'*-dihydroxyazobenzene (**89**), the 1-(2-hydroxyphenylazo)-2-naphthols (**90**), or the 1-phenyl-3-methyl-4-(2-hydroxyphenylazo)-5-pyrazolones (**91**). These compounds exist predominantly in the quinone hydrazone (**92** and **93**) and ketone hydrazone (**94**) forms, respectively (Section

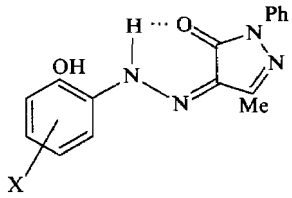
58.2.3.2), and Pfitzner concluded that all gave N_α copper and nickel complexes derived from these tautomeric forms.



(92)

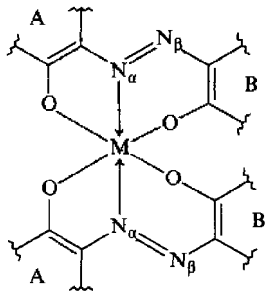


(93)

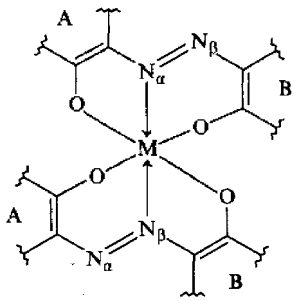


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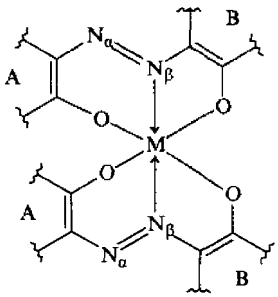
(b) Chromium and cobalt complexes. In the case of 2:1 cobalt(III) and 2:1 chromium(III) complexes of unsymmetrical *o,o'*-dihydroxyazobenzene compounds, three $N_\alpha-N_\beta$ isomers (**95–97**) are possible. Pfitzner[79] demonstrated the formation of three products chromatographically when those *o,o'*-dihydroxydiarylazo compounds which formed N_α and N_β isomers with copper and nickel were converted to their 2:1 chromium(III) and 2:1 cobalt(III) complexes and concluded that these were the three $N_\alpha-N_\beta$ isomers. He did not state whether these were meridional or facial complexes but it is probable that they had the former configuration.



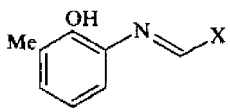
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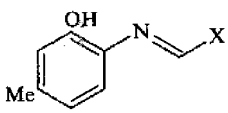
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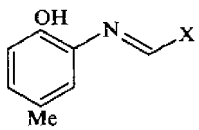
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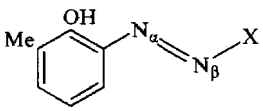
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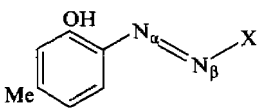
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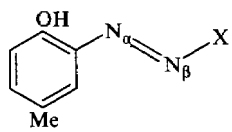
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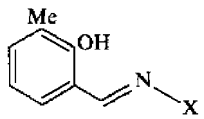
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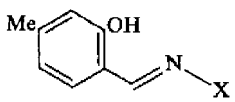
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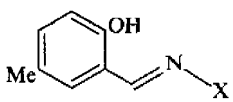
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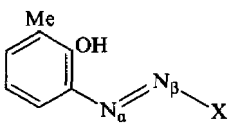
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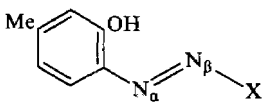
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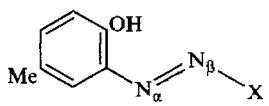
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(107)



(108)

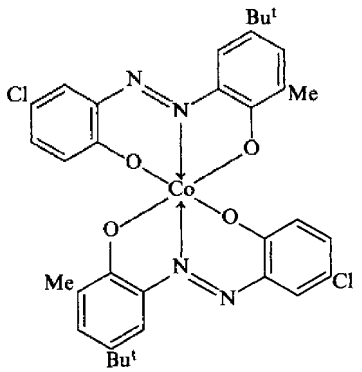


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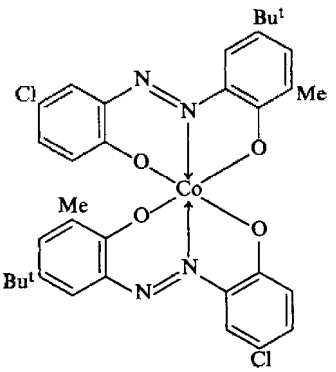
X = variously substituted 2-hydroxyphenyl

Support for the existence of $N_\alpha-N_\beta$ isomerism in 2:1 metal complexes of *o,o'*-dihydroxydiarylazobenzenes has been provided[80] by the application of proton magnetic resonance to the investigation of diamagnetic 2:1 cobalt(III) complexes. A systematic study was carried out of the chemical shifts of the methyl group proton signals in two series of related azomethines on conversion to their 2:1 cobalt(III) complexes. Cobalt complex formation by the first series (**98–100**) can be regarded as akin to N_α coordination (**101–103**) in the analogous azo series whilst cobalt complex formation by the second series (**104–106**) corresponds to N_β coordination (**107–109**) in

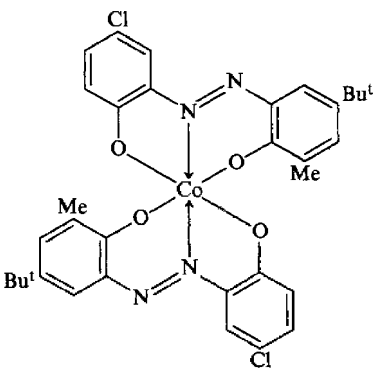
the azo compounds. This study demonstrated that the difference in the magnitudes of the shifts in the two classes of azomethines was sufficient to provide a diagnostic tool for distinguishing between the two types of coordination. The technique was, therefore, employed to study the conversion of the analogous methyl-substituted *o,o'*-dihydroxyazobenzenes to their 2:1 cobalt(III) complexes and demonstrated the presence of N_α–N_β isomers in the reaction mixtures. In one case the products were separated chromatographically and assigned the structures (**110**–**112**) on the basis of their ^1H NMR spectra.



(**110**)

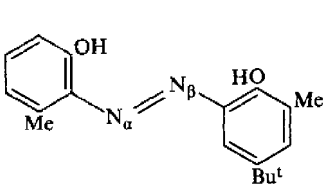


(**111**)

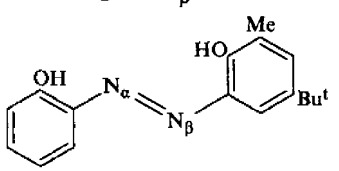


(**112**)

The relative proportions of N_α and N_β coordination varied considerably depending upon the structure of the *o,o'*-dihydroxyazo compound. Notably the azo compound (**113**) gave 92% N_β coordination whereas the azo compound (**114**) gave 70% N_α coordination. This is undoubtedly a result of the 'buttress' effect,[81] interaction between the 6-methyl group and the lone pair on the β-nitrogen atom of the azo group in (**113**) strongly favouring an N_β-coordinated configuration.

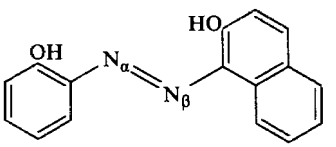


(**113**)

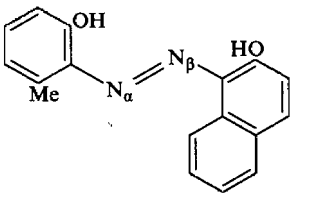


(**114**)

The influence of the buttress effect on isomer formation by tridentate azo compounds appears to have been ignored, but it can be invoked to account for many of the observed phenomena. For example, whilst the azo compound (**115**) forms only N_α complexes the separation of N_α and N_β isomers of the 2:1 cobalt(III) complex of (**116**) has been reported.[82] In the 1-(2-hydroxyphenyl-azo)-2-naphthol (**115**), steric interaction between the hydrogen atom in the 8-position of the naphthalene nucleus and the lone pair on the α-nitrogen atom of the azo group undoubtedly favours N_β-coordination. This effect is offset in (**116**) by steric interaction between the 6-methyl group and the lone pair on the β-nitrogen atom of the azo group, with the result that coordination to the metal can occur through either the α- or the β-nitrogen atom of the latter.



(115)

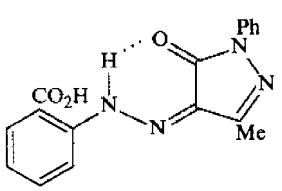


(116)

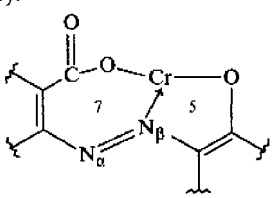
(ii) Geometrical isomerism

In 1939, Drew[83] proposed structures for 2:1 chromium complexes of *o,o'*-dihydroxydiarylazo and *o*-carboxy-*o'*-hydroxydiarylazo compounds in which the two dyestuff molecules were mutually perpendicular and octahedrally coordinated to the central chromium ion (**81**). Pfitzner[71] independently arrived at the same conclusion and 2:1 chromium complexes having this equatorial or meridional (*mer*) configuration have been described[84] as Drew–Pfitzner types. This configuration permits only an enantiomeric pair of isomers.

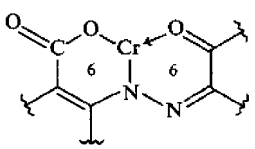
In 1941, Pfeiffer[85] succeeded in separating the 2:1 chromium complex of 1-phenyl-3-methyl-4-(2-carboxyphenylazo)-5-pyrazolone (**117**) into two isomers. In this case the possibility that these were N_α–N_β isomers was effectively eliminated on two counts. First, the ligand exists predominantly in the ketone hydrazone form (Section 58.2.3.3(i)) strongly favouring N_α coordination and, second, the formation of an N_β isomer (**118**) involves a complex containing annelated five- and seven-membered chelate rings. This is a highly unfavourable situation compared with that in the N_α isomer (**119**) which contains two annelated six-membered chelate rings. Accordingly Pfeiffer formulated his products as octahedral complexes in which the donor atoms of each azo compound were situated at the apices of an equilateral triangle forming the face of the valency octahedron of the chromium ion (**82**). Chromium complexes having this facial (*fac*) configuration have been described[3c] as Pfeiffer–Schetty types and present the possibility of four enantiomorphic pairs and one centrosymmetric isomer (Figure 1).



(117)



(118)

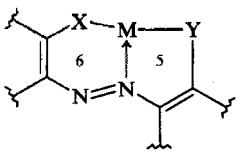


(119)

A further 20 years elapsed before further information became available when Schetty[86] published the first of a series[87] of papers on this subject in which he described the chromatographic separation of the 2:1 chromium complex of the *o*-carboxy-*o'*-hydroxydiarylazo compound 1-(2-carboxyphenylazo)-2-naphthol into four components. These had the same me empirical formula but different electronic spectra and solubility properties and, possibly most importantly from the point of view of the dyestuff chemist, each isomerized readily in solution to give an equilibrium mixture of the four components. In marked contrast, only one component was detected when the *o,o'*-dihydroxydiarylazo compound 1-(2-hydroxyphenylazo)-2-naphthol was converted into its 2:1 chromium complex.

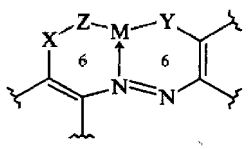
Following an examination of the 2:1 chromium complexes of further tridentate azo dyestuffs, with special emphasis on isomer formation, Schetty[88] came to the conclusions that (1) all those tridentate diarylazo dyestuffs which form annelated five- and six-membered chelate rings with the metal ion give complexes (**120**) having a *mer* configuration, and (2) those dyes which form two annelated six-membered chelate rings give complexes (**121**) having a *fac* configuration. Support for this was provided by careful calculation of the inter donor atom distances and bond angles in the two classes of dyestuffs in relation to their 'fit' on a right angled isosceles triangle or on an equilateral triangle, respectively. In the special case of unsymmetrical 2:1 chromium complexes derived from one molecule each of an *o,o'*-dihydroxydiarylazo and an *o*-carboxy-*o'*-hydroxydiarylazo compound, *e.g.* (**122**), it was found that meridional complexes were formed.

Schetty related his rules only to diarylazo dyestuffs and demonstrated that *o*-carboxyarylazopyrazolones formed both facial and meridional complexes. He attributed this to the greater distance between the two oxygen donor atoms in these compounds than in the corresponding



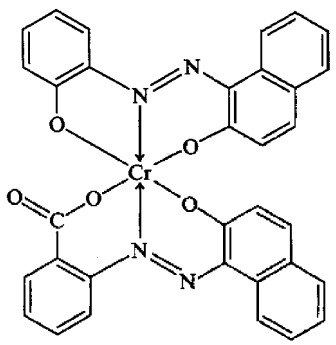
(120)

X	*Y*
O	O
NH	O
NPh	O
$N(SO_2R)$	O



(121)

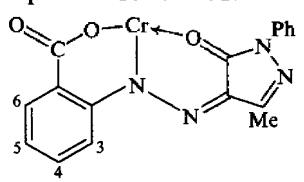
X—*Z*	*Y*
CO_2	O
CO_2	NH
$SO_2N(COPh)$	O
$CON(SO_2Ph)$	O



(122)

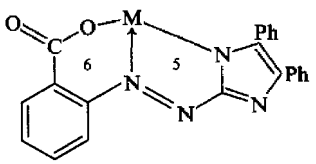
o-carboxy-*o*′-hydroxydiarylazo compounds, the result being that neither the facial nor the meridional form was especially favoured.

The influence of substituents on the types of complex formed by variously methyl-substituted *o*-carboxyarylazopyrazolones (**123**) is, however, seen as being very significant. Thus the buttress effect of a methyl group in the 3- or 6-position in (**123**) would effectively shorten the distance between the two oxygen donor atoms in the ligand, thereby favouring the formation of a *fac* complex. No such effect is exerted by a methyl group in the 4- or 5-position in (**123**) and *mer* complexes are formed.

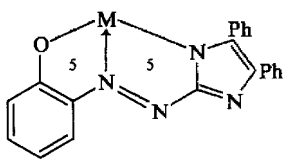


Facial complexes: 3-Me, 6-Me
Meridional complexes: 4-Me, 5-Me

(123)



(124)

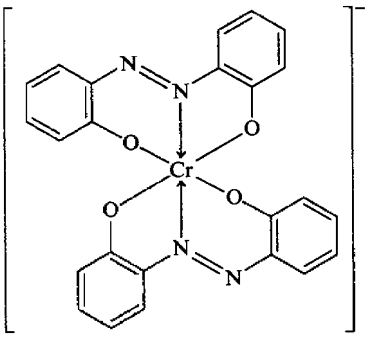


(125)

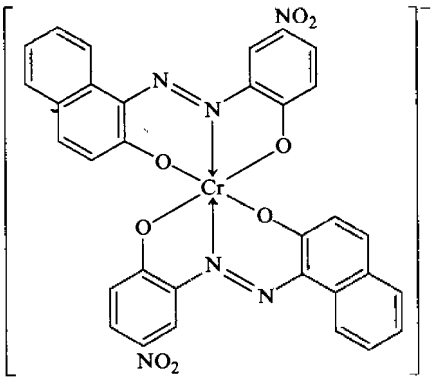
Clearly the distance between the donor atoms in ligands of this type is of prime importance in determining the configuration of their 2:1 chromium and cobalt complexes and this is further illustrated by dyestuffs derived from 4,5-diphenylimidazole. Both *o*-carboxyarylazo and *o*-hydroxyarylazo dyes of this class, which form 2:1 cobalt and 2:1 chromium complexes containing 6,5 and 5,5 annelated chelate ring systems, respectively (**124** and **125**), give complexes having the meridional configuration.

Support for Schetty's postulates has been provided by X-ray crystal structure determinations. Thus the 2:1 chromium complexes (**126**) and (**127**) of the two *o*,*o*′-dihydroxydiarylazo compounds 2,2′-dihydroxyazobenzene and 1-(2-hydroxy-4-nitrophenylazo)-2-naphthol, respectively, have been proved[89] to have meridional configurations, whilst the 2:1 chromium complex (**128**) of the *o*-carboxyarylazopyrazolone 1-(4-bromophenyl)-3-methyl-4-(2-methyl-6-carboxyphenylazo)-5-pyrazolone has been proved[90] to have a facial configuration.

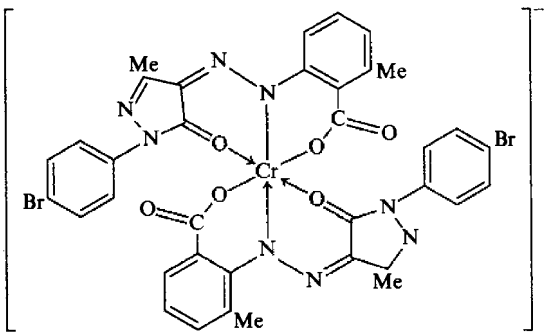
The rules governing this type of isomerism appeared, therefore, to be fairly clear but certain glaring exceptions soon became apparent. Thus, Idelson and Karady[91] converted the 1:1 chromium complex (**129**) of 1-phenyl-3-methyl-4-(2-hydroxy-4-sulfonaphth-1-ylazo)-5-pyrazolone into the sulfopiperidide and treated the product with pentane-2,4-dione. Chromatography of the reaction



(126)

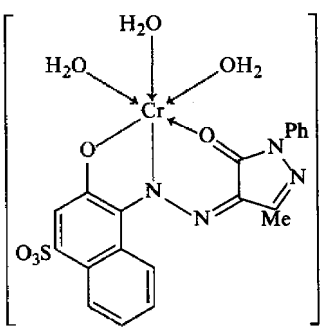


(127)

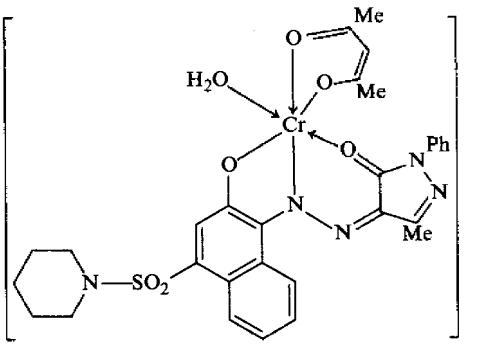


(128)

mixture gave three products having identical UV, visible and electronic spectra but significantly different X-ray powder diagrams. In each case, analytical results were in good agreement with the constitution (**130**).



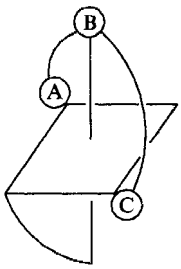
(129)



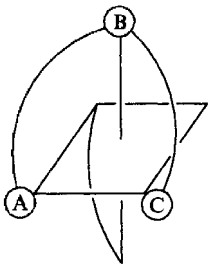
(130)

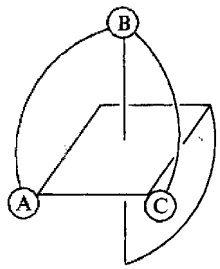
According to Schetty's rules the *o*-hydroxyarylazopyrazolone would be expected to form a meridional complex. In this case, however, only *dl* isomerism is possible in the product (**131**). On the other hand, three enantiomorphic pairs (**132**) are possible if the azo compound occupies a facial position. It was therefore concluded[91] that the chromium complex (**130**) must have a facial configuration. The similarity between the electronic spectra of this complex and the parent chromium complex (**129**) led to the conclusion that the latter also had a facial configuration. This is seen as a further example of the buttress effect, interaction between the hydrogen atom in the 8-position of the naphthalene nucleus and the lone pair on the non-coordinated nitrogen atom of the azo group effectively shortening the distance between the two oxygen donor atoms and thus favouring the facial configuration.

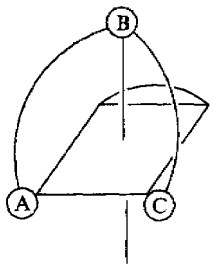
A similar argument can be applied to the results of later work by Idelson *et al.*[59] In this they prepared the chromium complex (**133**) by interaction of the 1:1 chromium complex of 1-phenyl-3-methyl-4-(2-hydroxy-4-cyanonaphth-1-ylazo)-5-pyrazolone and diethylenetriamine and by reaction of the azo compound with [Cr(CO)$_3$dien]. Identical products were obtained and, since the diethylenetriamine occupies[9] a facial position in [Cr(CO)$_3$dien], it was concluded that the complex (**133**) had a facial configuration. Similarly, the reported[77] separation of isomeric 2:1 chromium complexes of 2-amino-6-(2-hydroxy-6-nitro-4-sulfonaphth-1-ylazo)-5-naphthol-7-sulfonic acid is



(131)

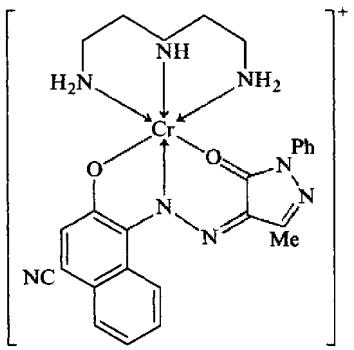




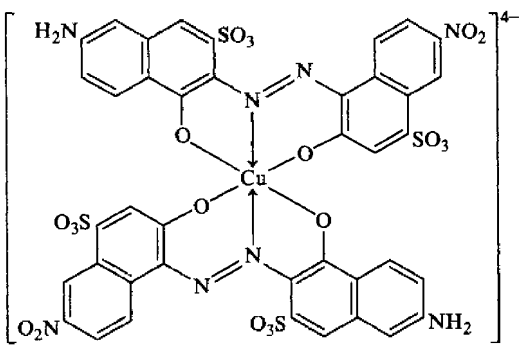


(132)

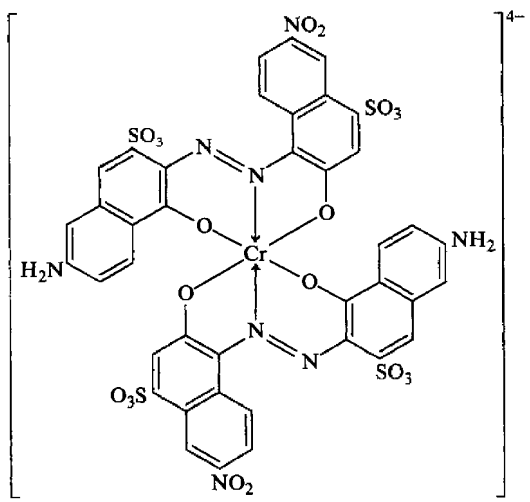
undoubtedly due to buttressing effects forcing the azo compound to adopt a facial configuration on the chromium ion. Thus interaction between the sulfonic acid group in the 3-position of the naphthalene nucleus and the lone pair on the non-coordinated nitrogen atom of the azo group in (**134**) or between the hydrogen atom in the 8-position of the naphthalene nucleus and the lone pair on the non-coordinated nitrogen atom of the azo group in (**135**) must result in a shortening of the distance between the two oxygen donor atoms and favour facial coordination.



(133)



(134)



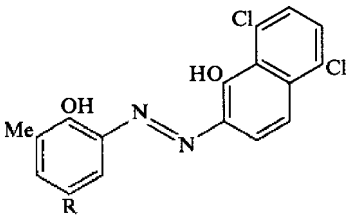
(135)

There is no doubt that Schetty's rules have a certain validity but great care must be exercised in their application since structural features of azo compounds other than their coordinating system can dramatically affect the geometry of the derived 1:2 chromium and cobalt complexes.

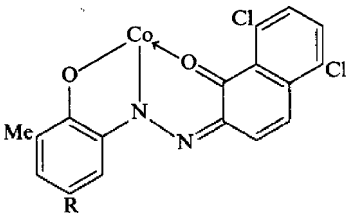
(iii) Azo–hydrazone tautomerism

Extension of the NMR studies described in Section 58.2.3.3(i)(b) to the compounds (**136**; R = NO_2 and R = Bu^t) led the authors to conclude that one N_α- and two N_β-coordinated cobalt complexes were produced. These were assigned the partial structures (**137**), (**138**) and (**139**), which involve coordination of the ligand in its azo form and in the two alternative hydrazone forms. In general (Section 58.2.3.2), azophenols exist exclusively in the azo form and serious doubts must exist regarding structure (**139**). Similarly, in view of the reported equilibration between the various isomers in solution, assignment of discrete tautomeric structures must be open to question. As-

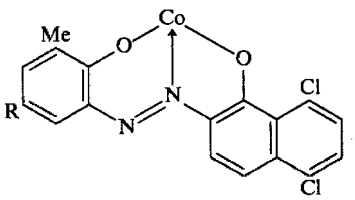
signment of these structures was based on the assumption that the complexes had meridional configurations and the buttressing effect of the methyl group in the phenyl moiety was neglected. In the absence of X-ray crystallographic data the alternative explanation that the products were, in fact, geometrical isomers of facially-coordinated complexes cannot, therefore, be excluded.



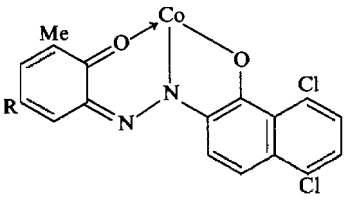
(136)



(137)



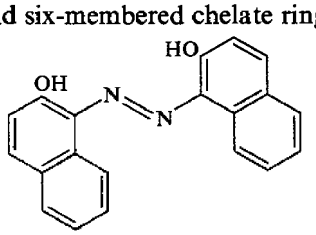
(138)



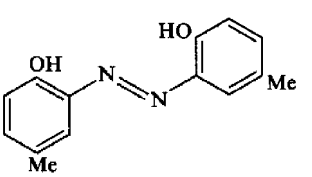
(139)

(iv) Isomerism arising from non-planarity in the ligand

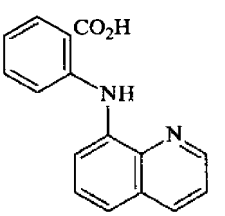
In 1970, Schetty[93] succeeded in isolating isomers of 2:1 chromium complexes derived from symmetrical *o,o'*-dihydroxydiarylazo compounds, in the cases of (**140**) and (**141**) no fewer than five products. These all had the same empirical formula and readily isomerized in solution to give the equilibrium mixture of isomers. In accordance with the rules which he had formulated earlier (Section 58.2.3.3(ii)), Schetty considered them to be meridional complexes and invoked azo-hydrazone tautomerism to account for isomer formation by dyes of this type. If both ligands in a 2:1 chromium complex are in the hydrazone form, this gives rise to the possibility of three conformers (Section 58.2.3.3(iii)). If one ligand is in the azo form and the other is in the hydrazone form, two conformers and their mirror images are possible. Only an enantiomeric pair is possible if both ligands are in the azo form. Thus six isomeric 2:1 chromium complexes and their mirror images were considered[93] to be possible as a result of azo–hydrazone tautomerism in the ligand. Schetty supported his conclusion with IR evidence and by demonstrating[94] that the non-planar tridentate ligand 8-(2-carboxyphenyl)aminoquinoline (**142**) forms three isomeric 2:1 chromium complexes. These were assumed to have meridional configurations since they involved annelated five- and six-membered chelate rings.



(140)



(141)



(142)

Again the lamentable lack of X-ray crystallographic evidence makes it impossible to draw firm conclusions regarding the validity of these structural assignments. However, it is highly probable that the buttressing effect would cause (**140**) to form facial complexes leading to geometrical isomerism. This argument cannot, however, be applied to (**141**).

The undoubted conclusion to be drawn from all these investigations is that various types of isomerism exist in 2:1 chromium(III) and cobalt(III) complexes of tridentate azo compounds. These have been reported to arise from N_α/N_β coordination, *fac/mer* coordination, azo/hydrazone tautomerism, and conformer formation resulting from non-planarity of the ligand in the hydrazone form. Taken together these present a formidable number of possibilities and, with the exception of those three cases where structures have been determined by X-ray crystallography, doubts must exist regarding structural assignments (Table 3). Indeed, even in those cases where structures have been determined by X-ray crystallography, queries have been raised[93] as to whether the ligand is in the azo or the hydrazone form. When these possibilities are extended to unsymmetrical 2:1

chromium and cobalt complexes derived from two different azo compounds, the problem becomes even more unmanageable.

Table 3 Isomerism in Metal Complexes of Tridentate Azo Compounds

Metal	*Type of isomerism*	*Evidence*
Copper and nickel	$N_\alpha-N_\beta$	Formation of two copper and two nickel complexes by unsymmetrical *o,o'*-dihydroxyazobenzenes[78]
Chromium and cobalt	$N_\alpha-N_\beta$	Detection of isomeric 2:1 chromium complexes;[79] proton magnetic resonance[80]
	Meridional/facial coordination	Isolation of isomeric 2:1 chromium and cobalt complexes;[86,87] limited X-ray crystallographic[89,90]
	Azo/hydrazone tautomerism	Proton magnetic resonance[80]
	Non-planarity due to azo/hydrazone tautomerism	Detection of five isomeric 2:1 chromium complexes of symmetrical *o,o'*-dihydroxydiarylazo compounds

So far as the dyestuffs chemist is concerned the problem is largely academic since, without exception, all the discrete isomers which have been reported rapidly revert to an equilibrium mixture in solution. They can therefore have no real relevance in a field of technology, dyeing, where they are invariably applied from solution. Nevertheless, a very important fact to emerge from these studies relates to the very facility with which interconversion of isomers does occur. This must proceed through a process of breaking and reforming bonds between the metal and the various donor atoms in the ligands. Presumably similar processes must operate with unsymmetrical 2:1 chromium and cobalt complexes derived from two different azo compounds, but it is very significant that these commercially very important dyestuffs do not undergo ligand redistribution in solution to give equilibrium mixtures comparable to those obtained by metallizing mixtures of tridentate azo compounds (equations 14–15).

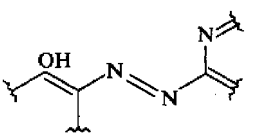
$$DH_2 + [Cr(H_2O)_6]^{3+} \xrightarrow{\text{low pH}} [DCr(H_2O)_3]^{+} \xrightarrow[\text{high pH}]{D'H_2} [DD'Cr]^{-} \qquad (14)$$

$$DH_2 + D'H_2 + [Cr(H_2O)_6]^{3+} \xrightarrow{\text{high pH}} [D_2Cr]^{-} + [D'DCr]^{-} + [D'_2Cr]^{-} \qquad (15)$$

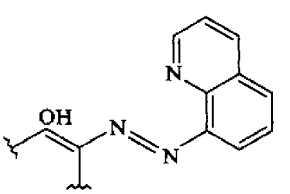
It must be concluded, therefore, that the ligands do not become completely detached from the metal ion in isomerization reactions. Comparable results have been observed in the isomerization[95] of potassium diaquodioxalatochromium(III) and the racemization[96] of optically active potassium tris(oxalato)chromium(III) when no exchange with free ligand in solution occurs. Thus, although it is not practicable to take advantage of the desirable properties of individual isomers of 2:1 chromium and cobalt complexes of tridentate azo compounds because of the facility with which such compounds isomerize in solution, the technically important unsymmetrical 2:1 complexes are capable of practical application because they show little or no tendency to disproportionate in solution.

58.2.3.4 Tridentate azo compounds containing hetero donor atoms

Tridentate metallizable azo dyestuffs containing one hetero donor atom suitably located for the formation of an annelated chelate complex are the subject of numerous patents, the most common being those containing a hetero nitrogen atom in a position adjacent (**143**) or *peri* (**144**) to the azo group. Typical examples include those listed in Table 4, which is by no means comprehensive. Their use as dyes for synthetic fibres including polyamides, polyesters and cellulose acetate has been widely claimed and, in general, they are converted to their metal complexes on the fibre by aftertreatment with a suitable metal salt. One interesting application of dyes of this type is in the dyeing of polypropylene.

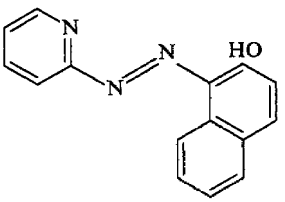
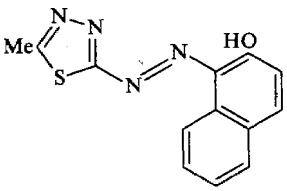
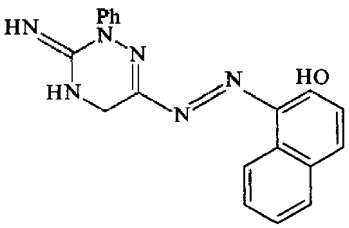
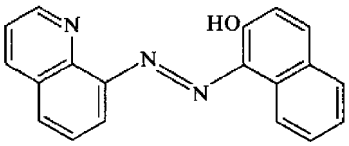
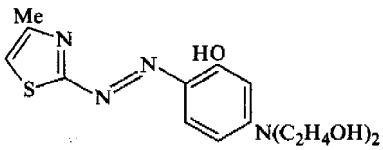
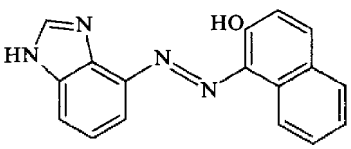
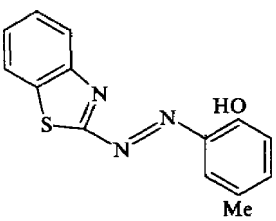


(143)

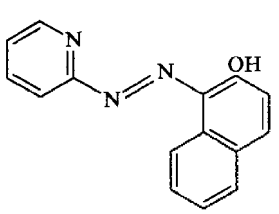


(144)

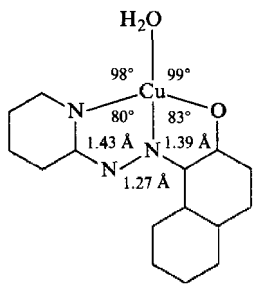
Table 4 Tridentate Azo Dyestuffs Containing Heterocyclic Nitrogen Donor Atoms

Typical azo compound	*Ref.*	*Typical azo compound*	*Ref.*
	97		101
	98		102
	99		103
	100		

The prerequisites for a fibre to be dyeable are, firstly, that it must be possible for the dyestuff to penetrate the fibre; secondly, the dyestuff must be able to migrate within the fibre to achieve a level dyeing; and thirdly, some interaction must take place between the dyestuff and the fibre so that the dye is not removed by subsequent processing, for example washing. Polypropylene fibres are hydrophobic and impenetrable by water-soluble dyes. Moreover, they contain no functional groups capable of serving as anchor sites for dyestuff molecules. Thus polypropylene presented the dyestuffs chemist with a number of novel problems. One method of overcoming these consists of incorporating in the polymer at the melt spinning stage a suitable metallic compound, for example aluminum stearate or the nickel complex of an alkylated *o,o'*-dihydroxydiphenyl sulfide or sulfone. The latter compounds serve a dual function in stabilizing the fibre against degradation by UV light and providing anchor sites for dyestuffs capable of combining with metal ions when applied to the fibre as aqueous dispersions. Various types of metallizable dyes have been described as being suitable for this application but the most favoured are tridentate types containing hetero donor atoms, *e.g.* (**145**). These are reported to give dyeings on nickel-modified polypropylene having good fastness to light and to wet treatments.



(**145**)



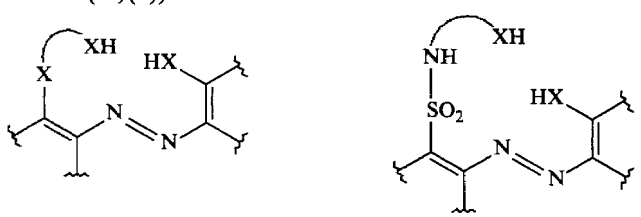
(**146**)

Certain azo dyes of this type, in particular pyridineazo-2-naphthol (PAN) and pyridineazoresorcinol (PAR), have been used in the spectrophotometric and titrimetric determination of metal

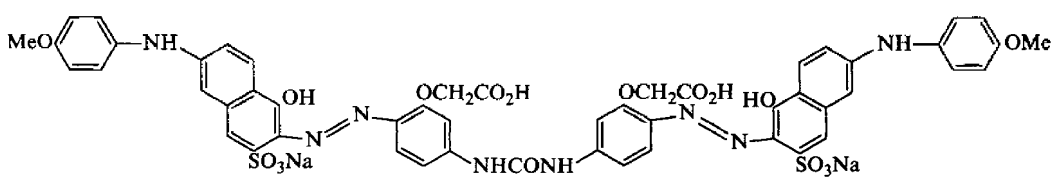
ions, as well as in their separation by solvent extraction techniques. These applications are discussed in detail in Chapter 10 and will not be considered further here. However, the anomalous nature of some of the published results of work in that field prompted Fernando and his coworkers[104] to carry out the X-ray crystal structure determination of the copper complex of pyridineazo-2-naphthol (**146**). The molecule is very nearly planar and has normal copper–nitrogen and copper–oxygen interatomic distances. Significantly (see Section 58.2.3.3(iii)), the double bond character of the azo group is preserved, showing that there is essentially no delocalization of electrons in the chelate ring containing the azo group, and only one nitrogen atom of the latter is involved in coordination to the copper ion.

58.2.4 Tetradentate Azo Compounds

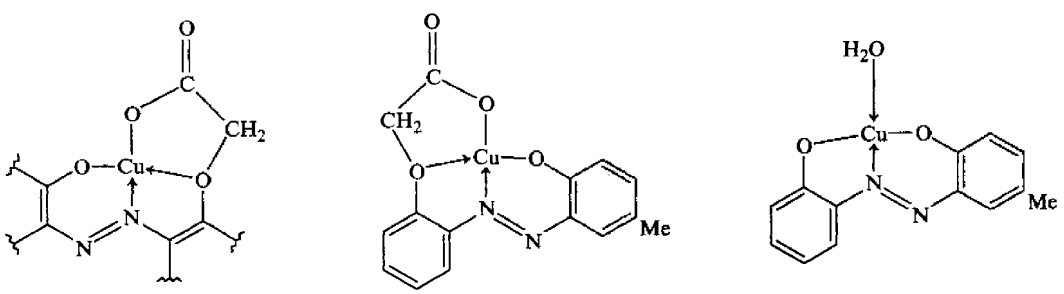
Metal complex dyestuffs derived from tetradentate azo compounds (**147**) have very limited commercial significance but merit brief discussion on chemical grounds. The first dyestuffs of this type to be used commercially contained the *o*-hydroxy-*o'*-carboxymethyleneoxydiarylazo system, *e.g.* (**148**). These were dyed on cotton and aftertreated with a copper salt to produce the copper complex dyestuff which was reported[71] to be a triannelated species (**149**). Formation of complexes of this type has been confirmed[105] in the case of 2-hydroxy-5-methyl-2'-carboxymethyleneoxyazobenzene, which yields the complex (**150**) on treatment with copper acetate under mild conditions. Under more severe conditions, however, the complex (**151**) is produced. Loss of the carboxymethyl group from dyes of this type has also been shown[105] to occur under dyebath conditions. This may be compared with the demethylation of *o*-methoxy-*o'*-hydroxydiarylazo compounds (Section 58.2.3.1(iii)(a)) under similar conditions.



(**147**) X = O, N



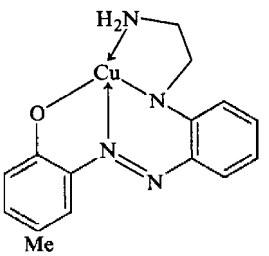
(**148**) Benzo Fast Copper Violet 3BL



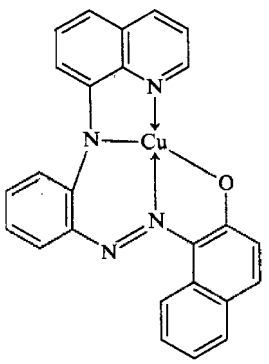
(**149**) (**150**) (**151**)

Copper complexes (**152**) of *o*-hydroxy-*o'*-(β-aminoethylamino)diarylazo compounds have been prepared[105] by the reaction of the corresponding *o*-chloro-*o'*-hydroxydiarylazo compounds and ethylenediamine in the presence of copper(II) ions (*cf.* Section 58.2.3.1(iii)(c)). Dyestuffs of this type have been evaluated on nylon but are reported to have very poor fastness properties. Copper complexes such as (**153**) have been prepared[106] by similar methods. Other, related tetradentate diarylazo compounds, *e.g.* (**154**), (**155**) and (**156**), are obtained by the reaction of a suitable diazonium salt with the appropriate diarylamine. Chromium(III) and cobalt(III) complexes of dyes of this type, in which the coordination sphere of the metal is completed by a colourless bidentate ligand such as ethylenediamine, salicylic acid or 8-hydroxyquinoline, are reported[107] to have dyeing properties on wool similar to those of the comparably charged 2:1 complexes derived from tri-

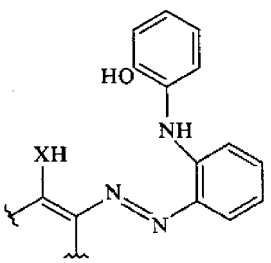
dentate azo compounds (Section 58.1). Thus, the singly negatively charged compound (**157**) dyes wool from near-neutral dyebaths in brilliant green shades having good fastness properties.



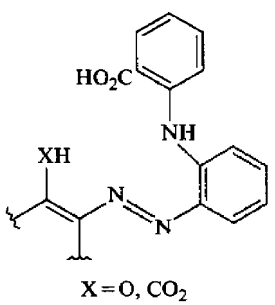
(**152**)



(**153**)

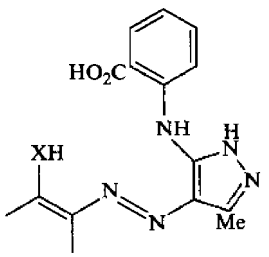


(**154**)

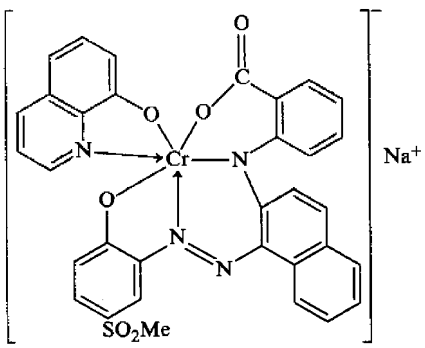


X = O, CO_2

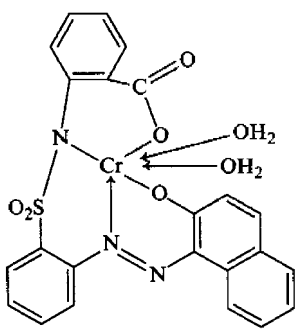
(**155**)



(**156**)



(**157**)



(**158**)

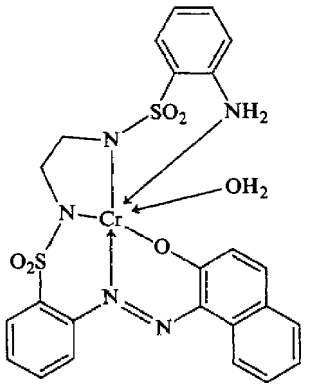
Tridentate diarylazo compounds containing *o*-hydroxy and *o'*-sulfonamido groups form metal complexes which are insufficiently stable to be of value as dyestuffs. Analogous tetradentate azo compounds are, however, reported[108] to give stable chromium(III) complexes, *e.g.* (**158**), although no dyestuff application of complexes of this type is known.

58.2.5 Pentadentate Azo Compounds

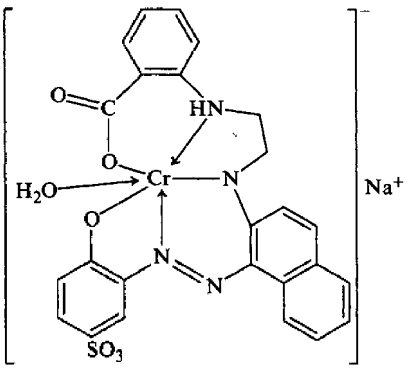
Few examples of pentadentate azo compounds capable of forming metal complexes containing four annelated chelate rings are recorded. Complexes such as (**159**)[109] and (**160**)[110] are, however, reported to be stable compounds and the latter is stated to dye wool in green shades from neutral dyebaths.

58.2.6 Hexadentate Azo Compounds

The preparation of chromium(III) and cobalt(III) complexes, such as (**161**) and (**162**), from hexadentate azo compounds has been reported[111] and, whilst the former are stated[112] to dye wool in brown shades having good wet-fastness properties and very good light-fastness, interest in complexes of these types has centred on their stereochemistry (Section 58.2.3.3(ii)). The former, which contain two annelated six-membered chelate rings involving the azo group, are analogous

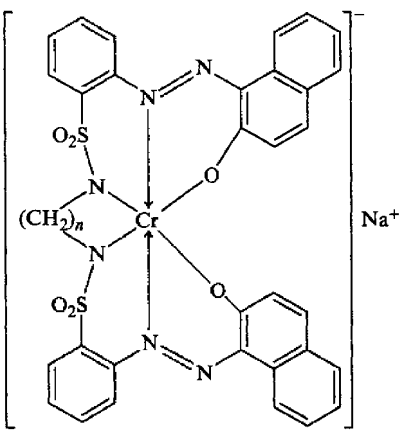


(159)

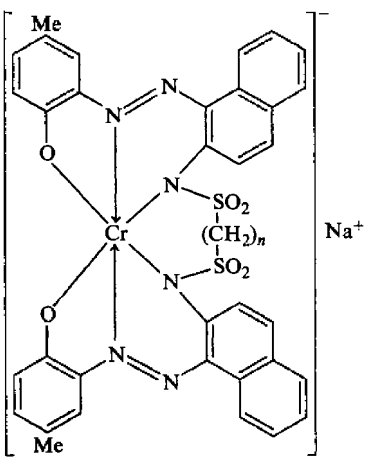


(160)

to complexes of *o*-carboxy-*o'*-hydroxydiarylazo compounds and, on the basis of the similarity of their electronic spectra to those of the 2:1 chromium(III) complexes of the latter ligands, have been assigned facial configurations. The influence of the size of the chelate ring involving the two sulfonamide groups on the stability of the complexes (**161**) is worthy of note. Thus the complexes (**161**; $n=2$) and (**161**; $n=3$), which contain five- and six-membered chelate rings, respectively, were stated to be very much more stable than the complex (**161**; $n=6$) which contains a nine-membered chelate ring.



(161)

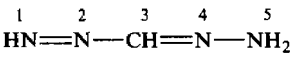


(162)

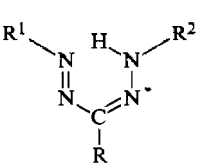
In contrast, complexes of the type (**162**), which contain annelated five- and six-membered chelate rings involving the azo group, were reported to form meridional complexes. In this case, however, the electronic spectra of the complexes (**162**; $n=2$) and (**162**; $n=3$) differed markedly from those of the 2:1 chromium(III) complexes of the corresponding tridentate azo compounds and this was attributed to strain in the seven- and eight-membered chelate rings involving the two sulfonamide groups. The electronic spectrum of (**162**; $n=10$), however, which contains a strainless 15-membered chelate ring involving the two sulfonamide groups, was identical with that of the 2:1 chromium(III) complex of the corresponding tridentate azo compound and this appears to be the principal evidence for the assignment of meridional configurations to these complexes. The complex (**162**; $n=10$) was also reported to be more stable than the complexes (**162**; $n=2$) and (**162**; $n=3$).

58.3 METAL COMPLEX FORMAZANS

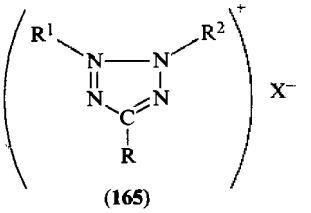
The formazans, which were first discovered[113] in 1892, are derivatives of the hypothetical parent compound (**163**). Various methods are available for their preparation[114] and a wide range of 1,3,5-substituted formazans (**164**) has been synthesized. These are usually brightly and intensely coloured and, following the observation[115] that 1,3,5-triphenylformazan readily formed copper, nickel and cobalt complexes, considerable effort was devoted[116] to developing metal complex formazans as dyestuffs. Very few such compounds have found commercial application, largely because of the ease with which formazans are oxidized[117] to the corresponding tetrazolium salts (**165**). This property has also led to some confusion regarding the nature of the metal complexes formed by variously-substituted formazans, which is not yet fully clarified.



(163)



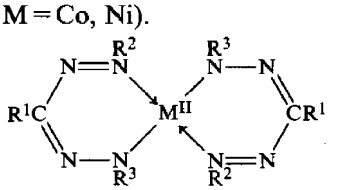
(164)



(165)

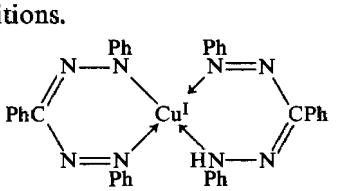
58.3.1 Bidentate Formazans

In 1941, Hunter and Roberts[115] reported the preparation of the copper(II), nickel(II) and cobalt(II) complexes (**166**; $R^1 = R^2 = R^3 = Ph$; M = Cu, Ni, Co) by the interaction of 1,3,5-triphenylformazan and the appropriate metal acetate in methanol. On the basis of their magnetic properties the products were assigned square planar structures by some workers[118] whilst others[119] concluded that this was improbable on steric grounds and favoured either distorted planar or grossly distorted tetrahedral structures. In marked contrast, however, certain 1,5-diaryl-3-acetyl-,[120] benzoyl-,[121] and ethoxycarbonyl-formazans[120] were reported to react with copper(II) acetate in ethanol to give copper(I) complex formazans having 1:1 stoichiometry. In the course of the reaction a portion of the formazan was oxidized and simultaneous elimination of the 3-substituent occurred to give 2,3-diaryltetrazolium salts.[121,122] With nickel(II) and cobalt(II) acetates, formazans of this type gave complexes having 2:1 stoichiometry (**166**; R^1 = Ac, CO_2Et; R^2, R^3 = Ph, C_6H_4hal, C_6H_4alkyl; M = Co, Ni).

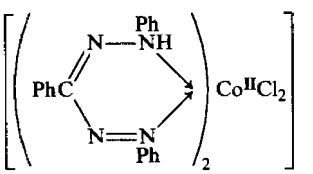


(166)

A more recent investigation[117] of the reaction of 1,3,5-triphenylformazan with copper(II) acetate has been carried out in which the former compound was extracted from a thimble into a boiling methanolic solution of a half-molar proportion of the latter. In the early stages of the reaction the highly-coloured formazan solution was decolourized immediately on contact with the copper(II) acetate solution as a result of oxidation to the tetrazolium salt. As the extraction proceeded, the reaction mixture developed an intense purple colour and a crystalline product was deposited. This was shown to be the neutral 2:1 copper(I) complex (**167**). The same product, which is presumed to have tetrahedral geometry, was obtained when 1,3,5-triphenylformazan reacted with copper(I) chloride in methanol in the presence of potassium acetate. When the reaction between 1,3,5-triphenylformazan and copper(II) acetate was carried out under the conditions employed by Hunter and Roberts, a product was obtained which gave analytical results in good agreement with the formulation (**166**; $R^1 = R^2 = R^3 = Ph$; M = Cu). The magnetic susceptibility of the product (1.4 BM), however, was considerably lower than the theoretical spin-only value for a complex of copper(II) and it was concluded that the product was a mixture of (**166**; $R^1 = R^2 = R^3 = Ph$; M = Cu) and (**167**) resulting from competition between metal complex formation and oxidation of the ligand under these conditions.



(167)



(168)

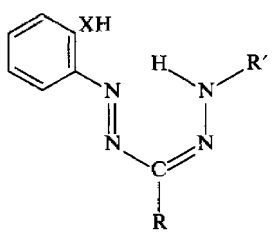
1,3,5-Triphenylformazan reacts with copper(II) chloride in methanol to give exclusively a tetrazolium salt; in the presence of atmospheric oxygen the reaction is catalytic. A similar reaction occurred when 1,3,5-triphenylformazan reacted with cobalt(II) chloride in methanol, even in the absence of air, but in this case a low yield of the octahedral cobalt(II) complex (**168**) was obtained. In contrast, 1,3,5-triphenylformazan reacted with cobalt(II) acetate in methanol to give (**166**; $R^1 = R^2 = R^3 = Ph$; M = Co) as the principal product. The complexes (**168**) and (**166**); $R^1 = R^2 = R^3 = Ph$; M = Co) may be compared with the analogous complexes obtained from bidentate diarylazo compounds (Section 58.2.2.1).

Oxidation of the formazan to a tetrazolium salt in the presence of cobalt(II) chloride is somewhat surprising, particularly as this occurred in the absence of air, but these results serve very effectively to demonstrate the sensitivity of the formazan towards oxidation in the presence of metal salts and provide an explanation for some of the conflicting results obtained by early workers in this field.

In general, metal complexes of bidentate formazans have low stability towards acids and, following the comparable work on metal complexes of azo compounds, Wizinger[116] was prompted to investigate tri- and tetra-dentate formazans in an endeavour to obtain metal complexes having enhanced stability.

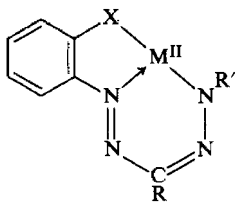
58.3.2 Tridentate Formazans

Copper and nickel complexes of the tridentate 1-(2-carboxyphenyl)-3,5-diphenyl- (**169**; X = CO_2; R = R′ = Ph) and 1-(2-hydroxyphenyl)-3,5-diphenyl- (**169**; X = O; R = R′ = Ph) formazans were prepared[118] by the interaction of the formazan and the appropriate metal acetate in alcohol and were assigned the three-coordinate structures (**170**; X = O, CO_2; R = R′ = Ph; M = Ni, Cu) since the diamagnetic nickel complexes were found to be unimolecular in benzene solution. Treatment of the nickel complex (**170**; X = O, R = R′ = Ph; M = Ni) with pyridine gave a violet crystalline adduct which was assigned the four-coordinate structure (**171**; X = O; R = R′ = Ph; M = Ni). A product similar to the latter could not be obtained from the nickel complex of 1-(2-carboxyphenyl)-3,5-diphenylformazan but nickel complexes of this type were obtained from both 1-(2-hydroxyphenyl)- (**169**; X = O, R = CN; R′ = Ph) and 1-(2-carboxyphenyl)- (**169**; X = CO_2; R = CN; R′ = Ph) 3-cyano-5-phenylformazans. In all three cases a considerable shade change occurred on going from the 'three-coordinate' complex to the pyridine adduct.



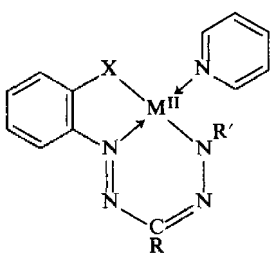
(169)

X	*R*	*R′*	
O	Ph	Ph	red
CO_2	Ph	Ph	orange red

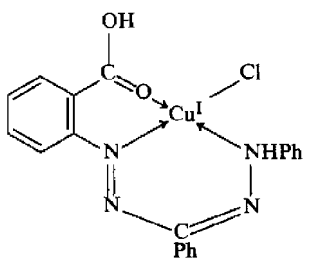


(170)

X	*R*	*R′*	*M*	
O	Ph	Ph	Cu	violet
O	Ph	Ph	Ni	brownish green
CO_2	Ph	Ph	Cu	violet
CO_2	Ph	Ph	Ni	leaf green



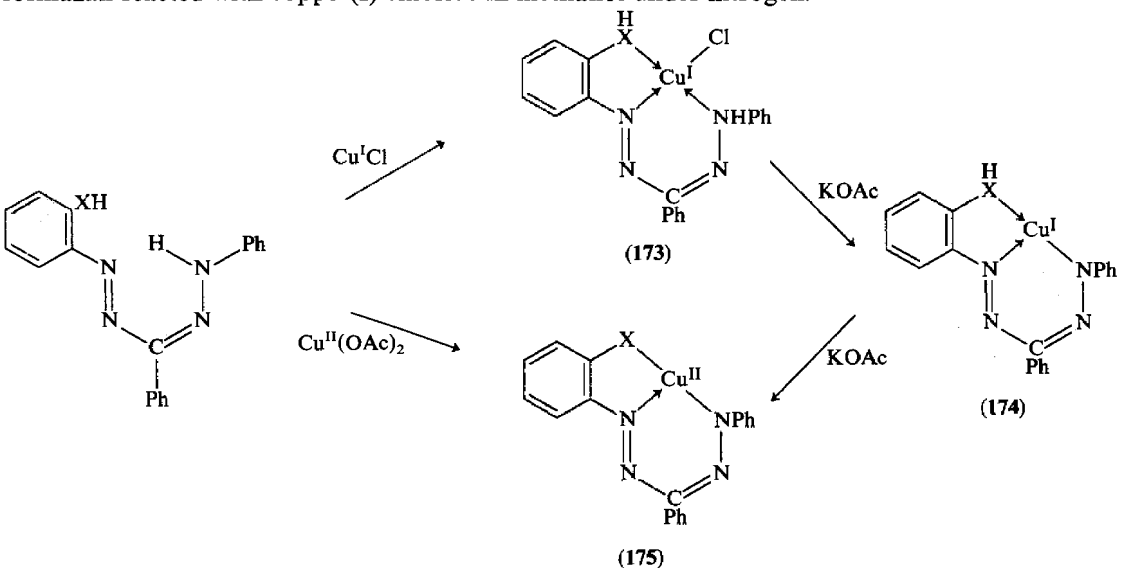
(171)



(172)

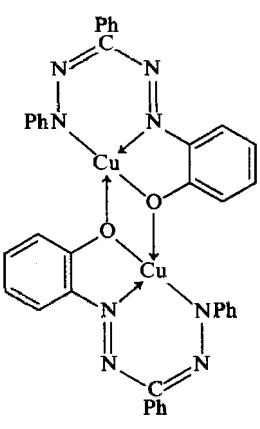
More recent work[117] has brought to light other, surprising, differences between 1-(2-carboxyphenyl- and 1-(2-hydroxyphenyl)-formazans and cast some light on the structures of their copper complexes. Like 1,3,5-triphenylformazan, both 1-(2-carboxyphenyl)- and 1-(2-hydroxyphenyl)-3,5-diphenyl-formazans were stoichiometrically oxidized to the corresponding tetrazolium salts by copper(II) chloride. With half-molar proportions of copper(II) chloride, however, the two formazans behaved quite differently. In the case of 1-(2-carboxyphenyl)-3,5-diphenylformazan, approximately 50% of the formazan was oxidized to the tetrazolium salt and the remainder reacted with the copper(I) chloride produced in this reaction to give a presumably tetrahedral copper(I) complex having 1:1:1 stoichiometry (**172**). The latter, also produced when 1-(2-carboxyphenyl)-3,5-diphenylformazan reacted with copper(I) chloride in methanol, was converted into a copper(II) complex which analyzed correctly for (**170**; X = CO_2; R = R′ = Ph; M = Cu) on treatment with

potassium acetate under nitrogen. In contrast, although approximately 50% of the formazan was oxidized to the corresponding tetrazolium salt when 1-(2-hydroxyphenyl)-3,5-diphenylformazan reacted with a half-molar proportion of copper(II) chloride under nitrogen, the remainder was converted into a copper(II) complex which gave analytical results in excellent agreement with the formulation (**170**; X = O; R = R′ = Ph; M = Cu). The latter was also produced when the parent formazan reacted with copper(I) chloride in methanol under nitrogen.

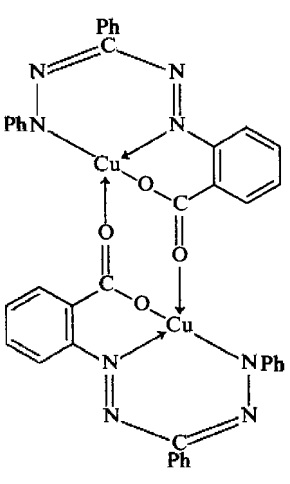


Scheme 6

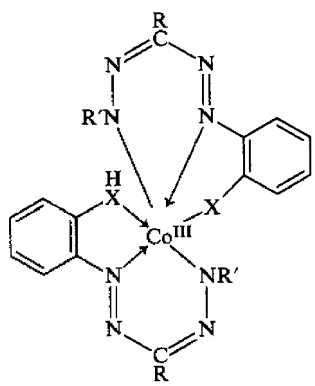
These results have several interesting implications regarding the effect of coordination on the acidity of the two ligands and the redox properties of the coordinated species. Thus (Scheme 6) it is reasonable to assume that the first step in the reaction between the two formazans and copper(I) chloride is the formation of a copper(I) complex (**173**). In the case of the 1-(2-carboxyphenyl)-formazan this is a stable, isolable species. Treatment with a salt of a weak acid results in proton loss from the coordinated ligand and, on the basis of the different behaviour of the two ligands, this is assumed to occur from the 5-nitrogen atom of the formazan. The oxidation potential of the resulting (**174**) is such that it spontaneously undergoes oxidation to (**175**) or, more likely, a protonated precursor which undergoes proton loss to give (**175**). Failure to detect a complex of the type (**173**) when the 1-(2-hydroxyphenyl)formazan reacted with copper(I) chloride in methanol under nitrogen suggests that it is a markedly stronger acid than is (**173**; X = CO_2) and immediately ionizes to (**174**; X = O). The oxidation in the conversion of (**174**) into (**175**) occurs at the expense of the ligand. So far as the structures of the copper(II) complexes of 1-(2-hydroxyphenyl)- and 1-(2-carboxyphenyl)-3,5-diphenylformazans are concerned, there can be little doubt on the basis of their magnetic properties[117,124] that they are the dinuclear, oxygen-bridged species (**176**) and (**177**), respectively.



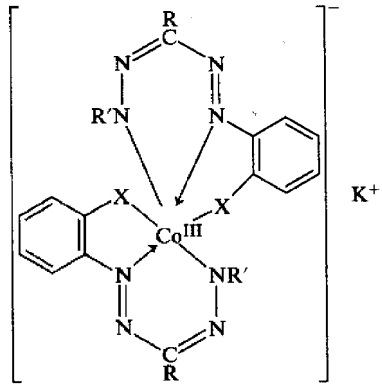
(**176**)



(**177**)



(178)



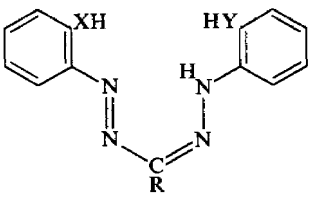
(179)

Tridentate formazans behave in a similar manner to tridentate azo compounds in giving cobalt(III) and chromium(III) complexes having 2:1 stoichiometry. In the case of the formazans, however, cobalt complexes (**178**) have been isolated[117] in which only one molecule of the ligand is fully deprotonated. Treatment of these with bases resulted in proton loss to give (**179**). For the cobalt complexes derived from 1-(2-carboxyphenyl)formazan, readily interconvertible isomers are formed[125], akin to those formed by *o*-carboxy-*o'*-hydroxydiarylazo compounds (Section 58.2.3.3(ii)). Again, interesting redox reactions have been observed[117] in the formation of these complexes and in the complexes themselves. Thus, when 1-(2-hydroxyphenyl)- and 1-(2-carboxyphenyl)-1,3,5-formazans react with cobalt(II) chloride to give the complexes (**178**; X = O; R = R′ = Ph) and (**178**; X = CO_2; R = R′ = Ph), respectively, the change in oxidation state occurs at the expense of the ligand, some of which is reduced. This compares with the similar behaviour of *o,o'*-dihydroxydiarylazo compounds (Section 58.2.3.1.ii), *o,o'*-diaminodiarylazo compounds (Section 58.2.3.2), 1,3-bis(2-pyridyl)-2,3-diazaprop-1-ene[126] and related compounds.[127] Surprisingly, however, some oxidation of the ligands to the corresponding tetrazolium salts also occurs during this reaction and the cobalt complexes themselves undergo oxidation in solution, giving the tetrazolium salts. It is, therefore, not surprising that although many patents exist on the use of complexes of tridentate formazans as dyes and pigments, they have found little or no commercial application.

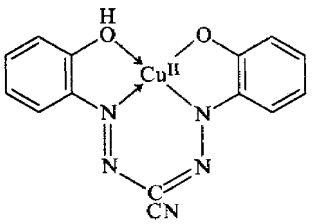
58.3.3 Tetradentate Formazans

The interaction of certain potentially tetradentate formazans, *e.g.* (**180**; X = Y = O; R = CN, Ph), (**180**; X = CO_2; Y = O; R = CN, Ph) and (**180**; X = Y = CO_2; R = CN, Ph), and nickel(II) and copper(II) salts was investigated by Wizinger[116,128] and his collaborators who were unable to say with certainty whether the complexes they obtained were bicyclic or tricyclic types. The stability towards acid of the products suggested that they were tricyclic but their colour supported their formulation as bicyclic types. A more recent study[129] strongly indicates that both types are formed, depending upon the structure of the parent formazan. Thus 1,5-bis(2-hydroxyphenyl)-3-cyanoformazan (**180**; X = Y = O; R = CN) reacted with copper(II) acetate under conditions comparable to those of the earlier workers to give a complex which gave analytical results in good agreement with a constitution comprising one molecule of doubly deprotonated formazan and one atom of copper. The magnetic susceptibility (1.8 BM) of the complex was within the range expected[130] for copper(II) complexes with strong covalent bonds and contrasted with that (1.3 BM) of the copper(II) complex of the tridentate 1-(2-hydroxyphenyl)-3,5-diphenylformazan (Section 58.3.2). On the basis of this and other spectral evidence the compound was formulated as the square-planar complex (**181**). The copper complex of 1-(2-hydroxyphenyl)-3-phenyl-5-(2-carboxyphenyl)formazan was formulated as (**182**) on similar evidence. Both (**181**) and (**182**) were readily deprotonated on treatment with a weak base such as potassium acetate to give the corresponding anionic complexes, thus affording a further example of the effect of coordination on the properties of a ligand, in this case dramatic enhancement of the acidity of a coordinated phenolic hydroxyl group.

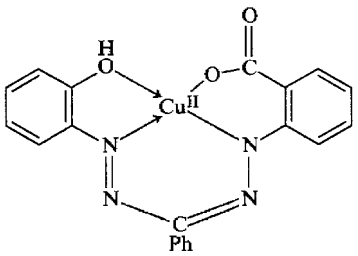
In marked contrast, 1,5-bis(2-carboxyphenyl)-3-cyanoformazan reacted with copper(II) acetate in methanol to give a complex containing water which could not be removed by conventional physical methods. Further, the product was not converted into an anionic complex on treatment with potassium acetate. The clear implication of this is that one carboxyl group is not coordinated to the copper ion and structure (**183**) is preferred to (**184**) proposed earlier.[129] It is, of course, possible that the complex has a dinuclear, oxygen-bridged structure of the type proposed for the



(180)

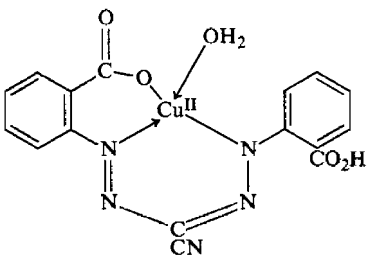


(181)

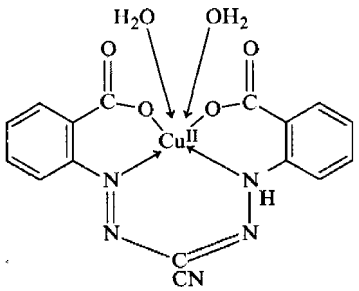


(182)

copper complex of 1-(2-carboxyphenyl)-3,5-diphenylformazan (**177**) and available evidence does not permit a firm distinction between the two possibilities.



(183)



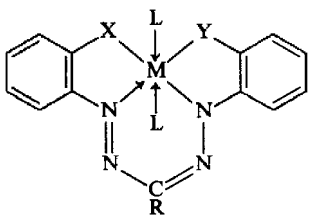
(184)

Comparison[117,129] of the behaviour of bidentate, tridentate and tetradentate formazans with copper(II) salts has effectively demonstrated that two competing reactions occur: copper complex formation (equation 16) and oxidation of the formazan to tetrazolium salt (equation 17).

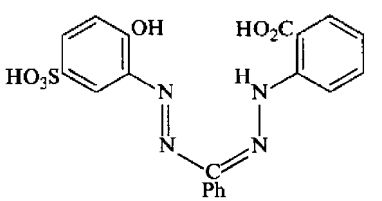
$$\text{formazan} + Cu^{II}X_2 \rightleftharpoons Cu^{II}\ \text{complex formazan} + 2HX \quad (16)$$

$$\text{formazan} + Cu^{II} \longrightarrow \text{tetrazolium salt} + Cu^{I} \quad (17)$$

The relative importance of these reactions is governed by the stability of the copper complex formazans towards acids. In the case of the bidentate formazans, the equilibrium (16) lies well to the left and such formazans are stoichiometrically oxidized to tetrazolium salts by copper(II) acetate. Tridentate formazans react with copper(II) acetate to give copper(II) complexes but are stoichiometrically oxidized to tetrazolium salts by copper(II) chloride. With the exception of 1,5-bis(2-carboxyphenyl)-3-phenylformazan, which is stoichiometrically oxidized to tetrazolium salt, the potentially tetradentate formazans which were examined react with copper(II) chloride to give mixtures of copper(II) complexes and tetrazolium salts. These results strongly suggest that 1,5-bis(2-carboxyphenyl)formazans function only as tridentate ligands in the formation of copper complexes. The reason for this marked difference in behaviour from that of the other potentially tetradentate 1,5-bis(2-hydroxyphenyl)- and 1-(2-hydroxyphenyl)-5-(2-carboxyphenyl)-formazans is undoubtedly steric hindrance.



(185) X = O, CO_2
Y = O, CO_2
M = Cr^{III}, Co^{III}
L = H_2O, NH_3, pyridine
R = Ph, CN, *etc.*



(186)

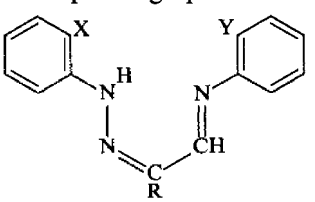
The preparation of chromium(III) and cobalt(III) complexes of tetradentate formazans in which the coordination sphere of the metal is completed by a variety of neutral ligands has been reported[116] and these (**185**) were claimed to be very stable towards acids. By analogy with copper complexes, however, some doubt must exist regarding the structures assigned to those complexes derived from 1,5-bis(2-carboxyphenyl)formazans. Various dyestuff and pigment applications have

been claimed in the patent literature for metal complexes of tetradentate formazans but few, if any, have found lasting commercial applications. This is a pity because of the intensity and brightness of their colours and is undoubtedly a result of extreme sensitivity of the formazan system towards oxidation to the tetrazolium salt.

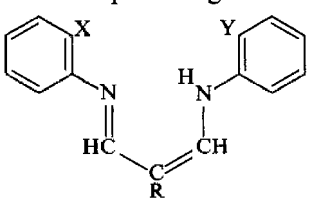
The intensity of the colours of metal complex formazans has, however, found applications in the analytical field; for example, it has been reported[131] that 1-(2-hydroxy-5-sulfophenyl)-3-phenyl-5-(2-carboxyphenyl)formazan (**186**) can be used for the detection of zinc at a concentration of 1:50000000.

58.3.4 Formazan Analogues

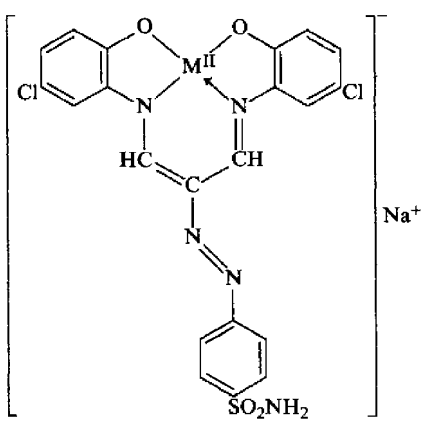
Glyoxalanil hydrazones (**187**) and malondialdehyde dianils (**188**) may be regarded as azomethine analogues of formazans and are reported[132] to behave in a comparable manner to the latter with regard to metal complex formation. In general, metal complexes of these compounds are much more feebly coloured than are those of the formazans. Copper and nickel complexes of the type (**189**) are, however, reported[133] to be suitable for dyeing wool and polyamides in shades varying from orange to violet depending upon the substituents in the parent ligand.



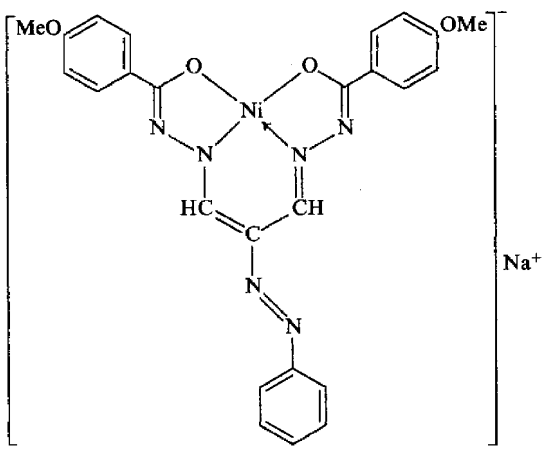
(**187**) X = H, OH, CO_2H
Y = H, OH, CO_2H
R = various substituents



(**188**) X = H, OH, CO_2H
Y = H, OH, CO_2H
R = various substituents



(**189**)



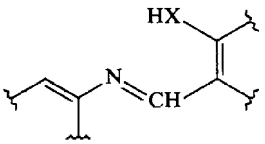
(**190**)

Interestingly, complexes of the type (**189**) were prepared by the interaction of *o*-aminophenols and arylazomalondialdehydes in the presence of copper(II) or nickel(II) salts. Replacement of the *o*-aminophenol by an acyl hydrazide resulted in the formation of complexes of the type (**190**), which are reported[134] to be suitable for dyeing synthetic fibres.

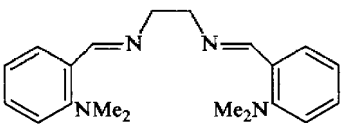
58.4 METAL COMPLEX AZOMETHINES

Azomethines bear a formal resemblance to azo compounds and many parallels exist in the coordination chemistry of the two series of compounds. Thus the bidentate azomethines (**191**) behave in a strictly comparable manner to the bidentate azo compounds (**20**) (Section 58.2.2.1). The isomeric, bidentate azomethines (**192**), however, form metal complexes which undergo very facile hydrolysis as a result of polarization of the azomethine linkage. The difference between the two types of complex is dramatically illustrated by the results of a study[135] of metal complex formation by the bis(azomethine) (**193**). This cannot function as a tetradentate ligand for steric reasons and reacts with copper, nickel and cobalt halides in cold ethanolic solution to form the five-coordinate complexes (**194**). Crystallization of these products from ethanol gives the five-

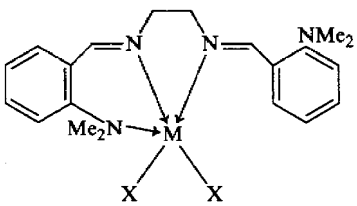
coordinate complexes (**195**), which are also formed when the parent (**193**) reacts with the metal halides in hot ethanolic solution. Since the parent ligand crystallizes unchanged from ethanol, these results clearly show that the exocyclic azomethine group is activated towards nucleophilic attack as a result of coordination to a metal.



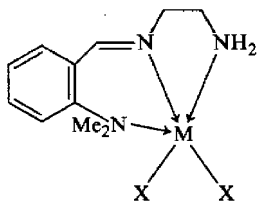
(**191**) X = O, NH (**192**)



(**193**)



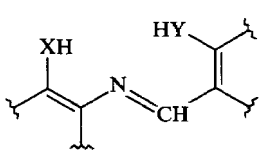
(**194**) M = Co^{II}, Ni^{II}, Cu^{II} X = Cl, Br



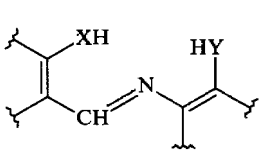
(**195**)

In general, the stability of metal complexes of bidentate azomethines of the type (**191**) is comparable to that of metal complexes of the analogous bidentate azo compounds (**14**) and is inadequate for practical application in the dyestuffs field. Limited numbers of such complexes have, however, been claimed to be suitable for pigment applications.

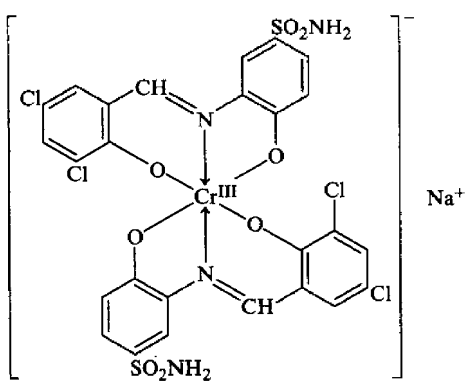
Metal complexes of a wide range of tridentate azomethines (**196** and **197**) containing a variety of donor functions (XH, YH), such as OH, NH_2, CO_2H and OCH_2CO_2H, have been examined[136] and, in general, their properties are similar to those of the analogous azo compounds. Their tinctorial strength is, however, considerably lower and this is compounded by the restricted range of shades which can be achieved. Their commercial application has, as a result, been very limited, a typical example being the dyestuff (**198**) which can be applied to wool and polyamide fibres from neutral dyebaths.



(**196**)



(**197**)



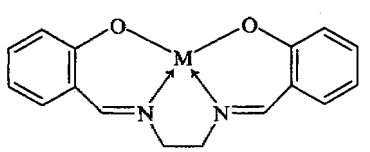
(**198**) Perlon Fast Yellow RS

Like the corresponding tridentate azo compounds, tridentate azomethines form 2:1 chromium complexes which, in some cases, exist in various isomeric forms. Since coordination is restricted to the nitrogen atom of the azomethine linkage, thus eliminating the possibility of $N_\alpha—N_\beta$ isomerism which exists in the analogous azo compounds, this has led to their being used as models in studies of the latter. This is discussed in detail in Section 58.2.3.3(i)(b).

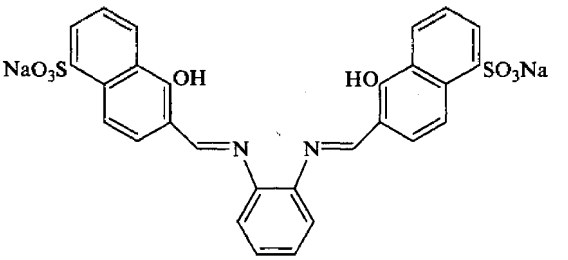
Metal complexes of tetradentate azomethines, *e.g.* (**199**), are reported[136] to have very high light-fastness but to be tinctorially weak and dull in hue. Despite this they are of technical interest as very fast yellow to brown pigments. They find no application as dyestuffs, however, because of these deficiencies; for example, the chromium complex of (**200**) gives dull, tinctorially weak dyeings on wool possessing poor wet-fastness properties.

58.5 METAL COMPLEXES OF *o*-HYDROXYNITROSO COMPOUNDS

Metal complexes of *o*-hydroxynitroso compounds are principally of historical interest since the iron complex of 1-nitroso-2-naphthol (Pigment Green B; CI 10006), which still finds commercial application as a green pigment, is the oldest fully synthetic metal complex dyestuff, dating back



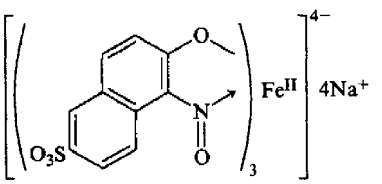
(199) M = Cu^{II}, Ni^{II}



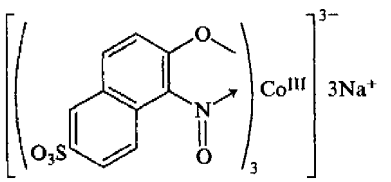
(200)

to 1885. The contemporary Pigment Green 12 (CI 10020) (**202**) which dyes wool in fast green shades from strongly acidic dyebaths was the forerunner of premetallized dyes of the Neolan and Palatine types (Section 58.1). It still finds limited application in the dyeing of wool, synthetic polyamides, paper and leather.

Some early confusion existed regarding the oxidation state of the iron in these complexes but it is now firmly established[137] that the iron(II) complex (**201**) is produced irrespective of whether the parent nitrosonaphthol reacts with iron(II) or iron(III) salts. Interestingly, the converse is true[138] of the cobalt complex (**202**) in which the trivalent oxidation state is favoured.

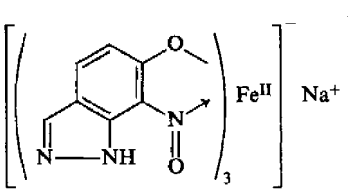


(201)

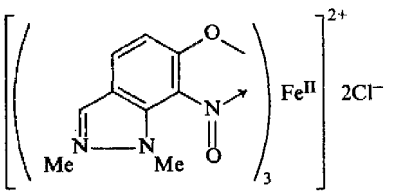


(202)

Iron(II) complexes of 7-nitroso-6-hydroxyindazoles (**203**) are sufficiently soluble in water to permit the dyeing of wool and polyamide fibres in green to olive shades having good fastness properties from weakly acidic dyebaths. Cationic iron(II) complexes (**204**) have also been prepared from quaternized indazoles of this type but have found little or no commercial application.

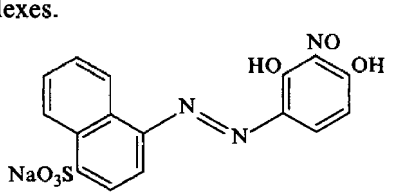


(203)

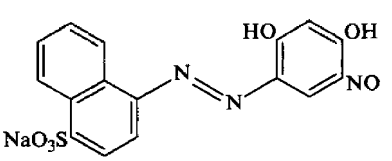


(204)

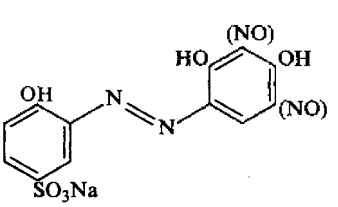
Iron, copper and nickel complexes of the products obtained by the nitrosation of arylazoresorcinols have been claimed[139] to dye leather in brown shades having excellent fastness to light. The structures of these products is open to debate since the position in which the resorcinol moiety is nitrosated (**205** or **206**) has not been established with any degree of certainty. Further, dyestuffs of this type, particularly those (**207**) derived from *o*-aminophenols, contain two metallizable systems and no information appears to be available regarding the stoichiometry and structure of their iron complexes.



(205)



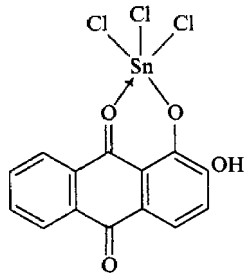
(206)



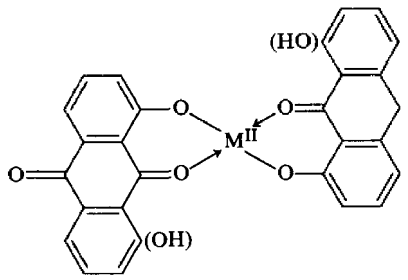
(207)

58.6 METAL COMPLEXES OF HYDROXYANTHRAQUINONES

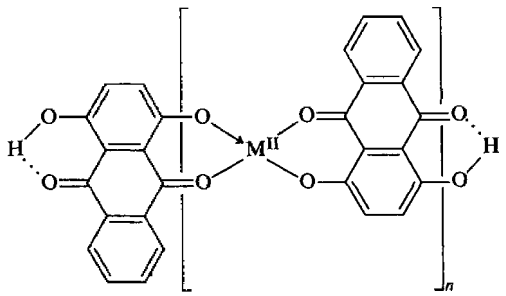
The classical forerunner of metallizable hydroxyanthraquinones was alizarin (**1**), which was widely used in the production of very fast, bright red shades on cotton by the mordant technique (Section 58.1). Early studies by Pfeiffer[140] demonstrated that metal complex formation involved the carbonyl group and the α-hydroxy group (**208**) rather than the two hydroxy groups and led to intensive research on metal complexes of 1-hydroxyanthraquinones and related compounds such as 8-hydroxynaphthoquinone. This is the subject of a number of reviews[3a,3c,141] and will only be considered briefly here.



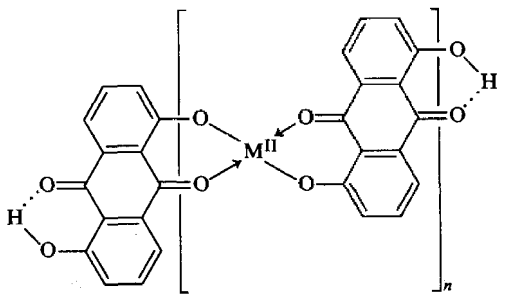
(**208**)



(**209**)

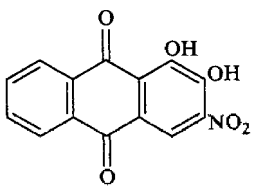


(**210**)

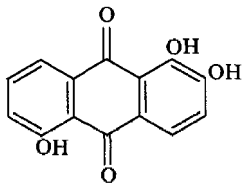


(**211**)

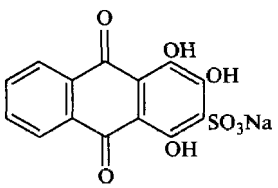
1-Hydroxy- and 1,8-dihydroxy-anthraquinones form neutral 2:1 complexes (**209**) with divalent metals such as copper and zinc, whilst 1,4- and 1,5-dihydroxyanthraquinones form polymeric complexes (**210**) and (**211**), respectively. The latter are virtually insoluble in a wide range of organic solvents and have been used for the mass pigmentation of synthetic polymers. The parent compounds have also found application as mordant dyestuffs, *e.g.* (**212**), (**213**) and (**214**).



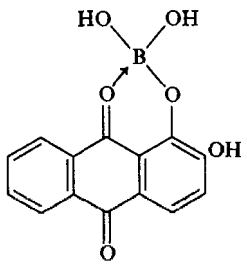
(**212**) Alizarin Orange A



(**213**) Brilliant Alizarin Bordeaux R



(**214**) Alizarin Red PS



(**215**)

Metal complexes of hydroxyanthraquinones are now only of historical interest in the dyestuffs and pigments field. Despite the very attractive shades and extremely good fastness properties of dyeings produced on cotton using the mordant technique with dyes of this type, they have been

superseded by other dyestuffs which can be applied to the fibre by simpler, more easily reproducible methods. The same is true of wool, and only a very few metal complexes of hydroxyanthraquinones are still used as pigments.

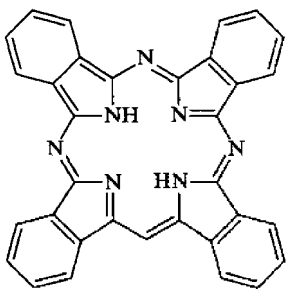
The ability of the 1-hydroxyanthraquinone system to form chelate complexes is, however, still employed in the synthesis of certain anthraquinone dyestuffs since it permits selective reactions to be carried out. Thus, treatment of the borate ester (**215**) of 1,2-dihydroxyanthraquinone with acetic anhydride yields 1-hydroxy-2-acetoxyanthraquinone, the 1-hydroxy group being protected against electrophilic attack as a result of its being involved in coordination to boron.

58.7 MACROCYCLIC METAL COMPLEXES

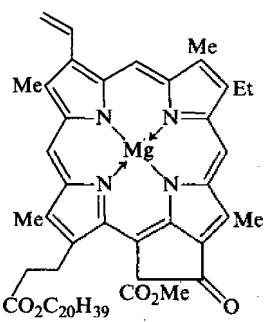
58.7.1 Phthalocyanines

Just as 2:1 chromium complexes of tridentate, medially metallizable azo dyes are the most important members of that class of dyestuffs, copper phthalocyanine (**13**) and its derivatives occupy a similar position in the field of macrocyclic metal complex dyes and pigments. Thus, although the individual compounds in this class are relatively few in number, in the pigment field alone they represent in total about one quarter of all the organic pigments manufactured and annual world production is measured in thousands of tonnes. This is attributable to three main factors. The first of these is their very beautiful bright blue to green shades and their high tinctorial strength. Their brightness is the result of the narrowness of the absorption peak in the visible region of the spectrum, the half band width being in the range 300–700 cm^{-1} compared with a half band width of some 5000 cm^{-1} for a typical azo dye. Further, the phthalocyanines fluoresce and fluorescence usually makes a colourant appear brighter. The second reason for their commercial importance is their remarkable chemical stability. Thus, copper phthalocyanine sublimes unchanged at 580 °C and can be dissolved in concentrated sulfuric acid without decomposition. The third factor is their excellent fastness to light, a vital property for many applications, for example in high quality automotive finishes. They are the subject of a number of publications and reviews.[3a,3d,142,143]

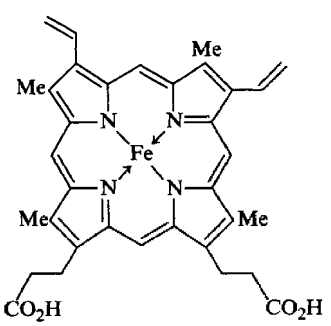
Following the observation in 1928 (Section 58.1) that a dark blue, water-insoluble, iron-containing crystalline byproduct was produced during the manufacture of phthalimide by the reaction of ammonia with molten phthalic anhydride in an enamelled iron vessel, the same product was obtained by passing ammonia gas into a mixture of molten phthalic anhydride and iron filings, confirming that the iron had originated from the reaction vessel. The intensity of the colour of the product and its remarkable chemical stability provoked considerable interest amongst dyestuff chemists and in 1934 Linstead,[144] at the request of ICI, elucidated its structure as the iron complex of (**216**). This was subsequently confirmed[145] by X-ray crystallography. Linstead named the new chromophore phthalocyanine (**216**) to indicate its origin and its colour.



(**216**)



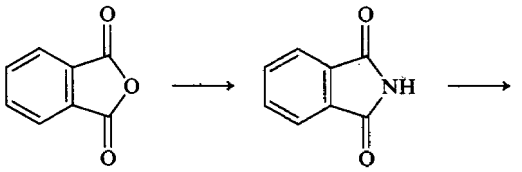
(**217**) chlorophyll a



(**218**) hemin

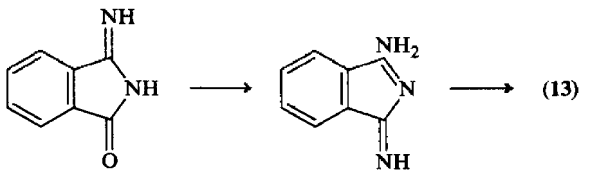
The phthalocyanines are structurally related to the naturally occurring porphyrins, the best known of which are probably chlorophyll (**217**), the green pigment essential for photosynthesis in plants, and hemin (**218**), the red colouring matter responsible for oxygen transport in humans. However, unlike the latter class, the highest intensity absorption band of the phthalocyanines occurs in the visible region of the spectrum and has an ε_{max} greater than 100 000, compared with an ε_{max} of only 10 000 in the visible region for the porphyrins. Further, although both phthalocyanines and porphyrins contain a cyclic, 16-atom system which is aromatic in character both according to the Hückel rule and its ability to sustain a ring current, the latter are very much less stable chemically and are easily destroyed by light, heat and mild chemical reagents. Replacement of any of the four *meso* nitrogen atoms in phthalocyanine by carbon results in a dramatic loss of stability. For these reasons, metal complex phthalocyanines are the only macrocyclic metal com-

plexes to find commercial application as dyes and pigments. Indeed, although many metal complexes of phthalocyanine have been synthesized, the copper complex is pre-eminent in this field.



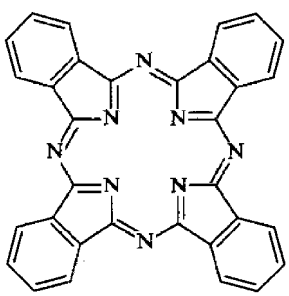
(219)

(18)



(220) (221)

Despite the expenditure of a tremendous amount of effort throughout the world, the two original methods employed in the manufacture of copper phthalocyanine are still used. In the first, a mixture of phthalic anhydride, urea and copper(I) chloride is heated in a high-boiling solvent such as nitrobenzene or trichlorobenzene in the presence of a catalytic amount of ammonium molybdate. The crude copper phthalocyanine is filtered off and the solvent recovered by distillation. The urea acts as a source of nitrogen and the first step in the overall reaction (equation 18) is conversion of phthalic anhydride to phthalimide (**219**) by ammonia liberated by the urea. More ammonia then converts the phthalimide to 1-keto-3-iminoisoindoline (**220**) and finally to 1-amino-3-iminoisoindolenine (**221**). All three intermediates have been isolated and identified. In the presence of copper chloride the 1-amino-3-iminoisoindolenine undergoes conversion to the copper complex of phthalocyanine.

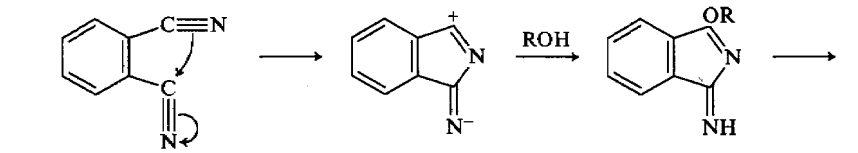


(222)

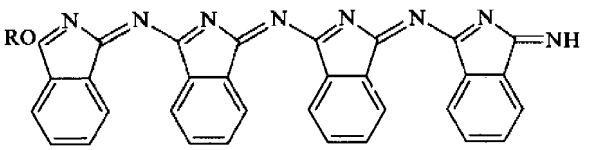
Mechanistics details of the cyclization process are meagre but it is probable that a template reaction[146] is involved in which the reactants are held in proper orientation for a particular reaction to occur as a result of their being coordinated to a metal ion. In this context it is noteworthy that, in the presence of nickel and cobalt chlorides, 1-amino-3-iminoisoindolenine undergoes cyclization to give the appropriate metal phthalocyanine whilst in the absence of the metal salts phthalocyanine is not produced. Further, when phthalic anhydride reacts with urea in the presence of cobalt chloride and a catalytic amount of ammonium molybdate under relatively mild conditions (160–175 °C), a cobalt complex of dehydrophthalocyanine (**222**) is produced which undergoes conversion to cobalt(II) phthalocyanine at higher temperatures or on treatment with relatively powerful reducing agents at room temperature.[147] It therefore appears likely that the metal ion serves as a template for the cyclic tetramerization of 1-amino-3-iminoisoindolenine to give dehydrophthalocyanine. The latter then undergoes facile reduction, the driving force for this being attainment of aromaticity in the central 16-membered ring.

In the second manufacturing process for copper phthalocyanine, phthalonitrile, copper(II) acetate and ammonium acetate are heated in the presence of a base, with or without a solvent such as pyridine. The mechanism of this has been less studied than that of the phthalic anhydride/urea reaction. It is, however, significant that metal-free phthalocyanine is manufactured by heating phthalonitrile with the sodium derivative of a high-boiling alcohol in an excess of the alcohol. This reaction is believed[148] to occur by the route outlined in Scheme 7, which is supported by the isolation of compounds of types (**223**) and (**224**). If this or a related mechanism operates in the

synthesis of copper phthalocyanine, it is still possible that the metal ion functions as a template at the cyclization stage.



(223)



(222) (13)

(224)

Scheme 7

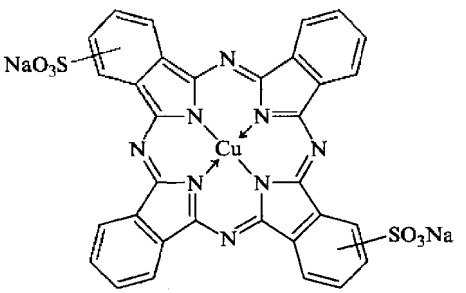
Copper phthalocyanine exhibits polymorphism, the two major polymorphs being the α-form and the greener, more stable β-form. All production methods for copper phthalocyanine yield coarse crystals of the β-form, unsuitable for pigmentary applications. These can be converted by reprecipitation from sulfuric acid or by grinding with sodium chloride into the metastable, finely particulate α-form, which is suitable for use as a pigment. It is also possible to obtain the β-polymorph in a fine particulate form suitable for pigmentary applications by grinding in the presence of additives such as fatty amines which inhibit the formation of the α-form. The redder β-form tends to be favoured by paint manufacturers whilst the α-form finds its major outlet in printing inks.

X-Ray and neutron diffraction studies of phthalocyanines have shown that the four benzene fragments interact only weakly with the 18 π-electron inner ring system, with the consequence that substituents in the benzene rings have only a minor effect on the colour of phthalocyanines. Nevertheless, valuable greenish blue and green pigments are provided by halogenated derivatives of copper phthalocyanine. These can be prepared from the appropriate halogenated phthalic anhydrides but halogenation of copper phthalocyanine itself is generally the preferred method. As many as 15–16 chlorine atoms can be introduced into copper phthalocyanine and such a high degree of chlorination is necessary to achieve a green shade. The method by which this is accomplished serves very effectively to demonstrate the remarkable chemical stability of the copper phthalocyanine moiety. Thus chlorine is passed into a solution of copper phthalocyanine in a molten eutectic mixture of aluminum chloride and sodium chloride at temperatures up to 180–190 °C for upwards of 20 hours. The hot melt is then poured into water, hydrochloric acid is added, the mixture is stirred for 2 hours and the product is filtered off, washed and dried. Brominated copper phthalocyanines are desirably yellower in shade than the corresponding chlorinated products but it is extremely difficult to achieve complete bromination. However, a mixed bromo–chloro copper phthalocyanine containing about 11–12 atoms of bromine and 3–4 atoms of chlorine per molecule can be prepared and is considerably yellower than the corresponding chloro compound. This is manufactured by passing chlorine into a solution of copper phthalocyanine in a molten eutectic mixture of aluminum chloride and sodium bromide.

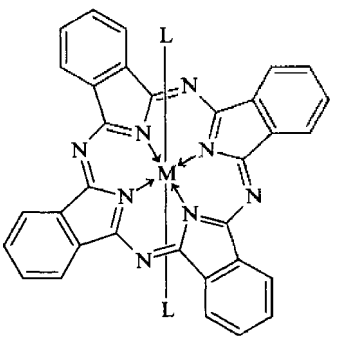
Copper phthalocyanine now finds only limited application in the dyestuffs field, principally in the dyeing of paper and cotton, largely because of technical improvements of direct dyes and the advent of fibre-reactive dyes. However, following the discovery of copper phthalocyanine, considerable effort was devoted to devising means of employing it as a dyestuff because of its brilliance of hue and high stability. This followed two discrete lines: chemical modification of copper phthalocyanine to endow it with suitable properties, and production of precursors capable of conversion to copper phthalocyanine within a textile fibre. The first of these is well documented to 1963 in the monograph of Moser and Thomas[143] and updated to 1971 in the review by Booth.[3d] It will not be discussed in detail here since it relates more to dyeing technology than to coordination chemistry. It is, however, worth brief comment since it serves further to illustrate the quite remarkable chemical stability of copper phthalocyanine.

The first prerequisite for copper phthalocyanine-based dyestuffs was the production of water-soluble derivatives and this was made possible by the resistance of the parent compound to chemical degradation. Thus, treatment of copper phthalocyanine with 26% oleum first at 45 °C and then at 60 °C for 12 hours gives the water-soluble disulfonic acid (**225**) which was the first commercial

phthalocyanine dye (CI Direct Blue 86). The wash fastness of dyes of this type is not good and further developments revolved around the use of sulfonamide groups as bridging groups between the copper phthalocyanine moiety and some other grouping, the introduction of which suitably modifies dyeing properties. Thus, from one to four chlorosulfonyl groups can be introduced into copper phthalocyanine by treatment with chlorosulfonic acid at temperatures of the order of 120–140 °C. Reaction of these substituents with one amino group of a diamine such as an alkylenediamine, phenylenediamine or phenylenediaminesulfonic acid provides intermediates capable of further modification by, for example, the introduction of a fibre-reactive group through acylation of the pendant free amino group with cyanuric chloride. Pendant amino groups are also important because of their ability to provide water-soluble derivatives of copper phthalocyanine through quaternization. Other water-soluble, quaternary compounds of copper phthalocyanines are derived from chloromethylated derivatives of the latter. The original method for the production of these involved the interaction of bis(chloromethyl)ether or paraformaldehyde and copper phthalocyanine in an aluminum chloride melt. Alternative processes involve reaction of paraform with copper phthalocyanine dissolved in a mixture of chlorosulfonic and sulfuric acids, or reaction with bis(chloromethyl) ether in sulfuric acid solution. Reaction of chloromethylated derivatives of copper phthalocyanine with thiourea yields water-soluble isothiouronium salts which can be insolubilized within cotton fibre by an alkaline treatment to give very fast dyeings.

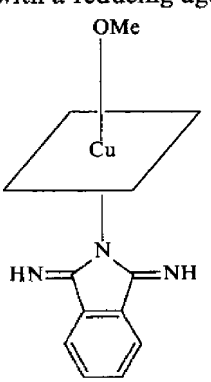


(225)

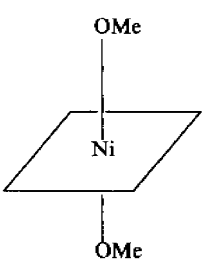


(226)

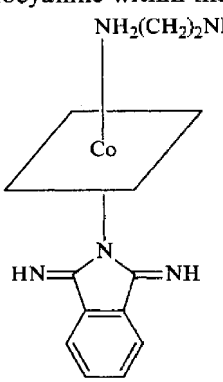
The alternative approach to the colouration of textile fibres with metal, especially copper, complex phthalocyanines involved synthesis of the latter within the fibre from suitable water-soluble precursors. This development has been described in some detail by Vollmann[148] and followed two main approaches. The first of these was based on the production of hexacoordinate metal (copper, nickel and cobalt) complexes (**226**) of dehydrophthalocyanine, *e.g.* (**227**–**229**). These are prepared either by the oxidation of metal phthalocyanines under mild conditions using, for example, nitric acid or halogens in alcoholic solvents, or directly from phthalimide or 1-substituted 3-iminoisoindolenines and metal salts, again under mild conditions. For example, the copper complex (**227**) is reported to be obtained in good yield by heating a methanolic solution of 1,3-diiminoisoindolenine and copper acetate (in a molar ratio of about 5:1) under reflux for 15–20 hours with continuous removal of ammonia. Metal complex dehydrophthalocyanines of these types are applied to cellulosic materials as solutions in solvent/water mixtures and the material is then treated with a reducing agent to generate the metal phthalocyanine within the fibre.



(227)



(228)



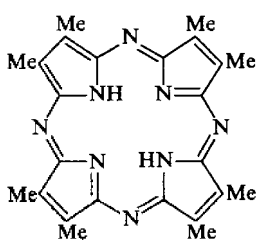
(229)

The second approach stemmed from the observation that a 1-substituted 3-iminoisoindolenine (**223**) was a probable intermediate in the synthesis of copper phthalocyanine from phthalonitrile. This led to the development of processes for the manufacture of 1,3-diiminoisoindolenine and its

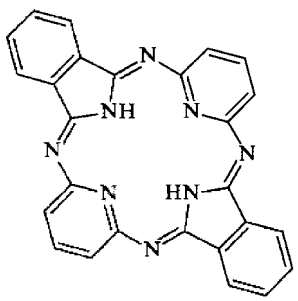
use as a convenient precursor for the formation of copper phthalocyanine within a textile fibre. By appropriate substitution of the 1,3-diiminoisoindolenine, shades ranging from blue to green can be obtained. In the dyeing process the 1,3-diiminoisoindolenine and a copper or nickel salt or complex, frequently derived from glycine or a derivative, are impregnated in the cellulosic textile material from a solvent/water mixture. The material is then heated to drive off the water when copper or nickel phthalocyanine are produced within the fibre, probably by a template reaction. Dyeings having excellent fastness properties can be achieved in this way but the method suffers from the same problems as the mordant dyeing method (Section 58.1) and shade matching is difficult.

58.7.2 Others

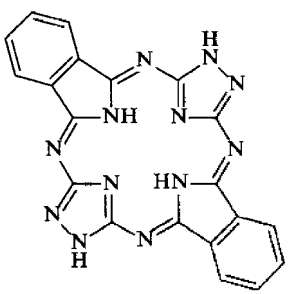
Great efforts have been made to produce macrocyclic metal complexes having properties comparable to those of the phthalocyanines but covering the rest of the visible spectrum, in particular the red. Whilst a variety of macrocyclic complexes has been prepared and numerous patents exist, no products of commercial importance have emerged. This is true of compounds formally related to the phthalocyanines including the porphyrazines, *e.g.* (**230**), the nickel complex of which is reported[150] to be a purple pigment, and the hemiporphyrazines such as (**231**),[149] (**232**) and (**233**),[150] metal complexes of which are stated to be brownish orange to green pigments. Compounds of this type are prepared by the reaction of 1-amino-3-iminoisoindolenine with the appropriate diamine. The nickel complex (**234**), prepared[151] by the condensation of *o*-phenylenediamine and 3-formylpentane-2,4-dione in the presence of nickel salts, is stated to be a red-violet pigment but finds no technical application.



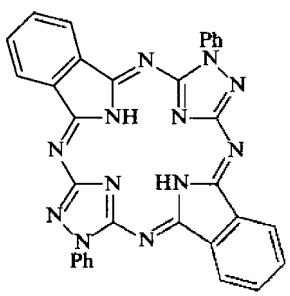
(230)



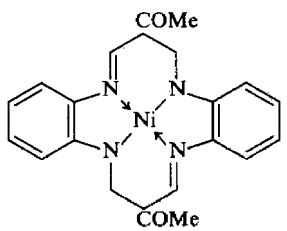
(231)



(232)



(233)



(234)

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59

Photographic Applications

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59.1 INTRODUCTION

Coordination chemistry is important not only in conventional silver halide-based photography but also in a variety of other imaging systems. This review covers the use of coordination com-

pounds in photography and in such areas as electrophotography and photothermography. Much of the information is available only in patents. We have tried to select the major patents in a particular area to provide appropriate references to the system(s) being discussed. 'The Theory of the Photographic Process' edited by James[1] is the major reference work for conventional photographic imaging. Less conventional imaging systems are discussed in a number of other texts.[2–5]

The coverage has been limited to the applications of coordination compounds or of the coordination chemistry of relatively soluble ligands and metal species. Numerous chemical agents in photographic systems function by means of adsorption on silver halide grains and silver metal surfaces. Such chemical interactions lie outside the confines of coordination chemistry defined for this work and have not been discussed.

59.2 CONVENTIONAL SILVER HALIDE-BASED PHOTOGRAPHY

59.2.1 Silver Halide and Silver Processes

59.2.1.1 Precipitation of silver halide grains

Making photographic emulsions (actually dispersions of silver halide microcrystals in a protective colloid, usually gelatin) is a complex technology requiring several steps.[6] These include: (1) forming a dispersion of the microcrystals (grains) in a solution of the protective colloid; (2) physical ripening to produce desired crystal sizes; (3) washing to remove soluble salts from the medium; (4) heating the emulsion, usually in the presence of chemical sensitizing agents, to increase light sensitivity — a process called digestion, chemical ripening or afterripening; (5) adding other agents such as sensitizing dyes, antifoggants or sensitizing agents, and hardeners.

Coordination compounds and coordination chemistry are involved in a number of these steps. Chemical sensitizing agents, antifoggants and stabilizers are discussed separately. This discussion concerns silver halide emulsion precipitation and physical ripening methods.

The silver halide grains are usually precipitated in the presence of gelatin by mixing solutions of halide salts and silver nitrate. The mixing is carefully controlled; temperature, concentrations of reagents, rates of addition and the sequence of addition are among the controlled variables. Gelatin provides not only a coatable, crosslinkable (hardenable) medium for spreading the emulsion, but also a special medium in which crystal growth is controlled and the grains remain suspended in the stable protective colloid, largely by means of complex adsorption and solvation effects. Natural trace contaminants of gelatin include sulfite and thiosulfate, and these can affect the precipitation and physical ripening.[7]

Physical ripening is brought about by the solvent action of silver ion complexing agents. During physical ripening the silver solvent permits the partial dissolution, recrystallization and growth of the microcrystals to produce the desired size and size distribution of grains. Emulsions precipitated under acidic or neutral conditions can be ripened in the presence of a large excess of halide ions; the partial dissolution of silver halide is brought about by the formation of complex ions such as $[AgX_2]^-$ (where X represents a halide ion). Another type of emulsion, the ammoniacal emulsion, is prepared by adding ammonium hydroxide during precipitation or ripening. Ammonia accelerates physical ripening by means of its ability to dissolve silver halide and produce complex ions such as $[Ag(NH_3)_2]^+$.

Although most emulsions are precipitated and ripened by the general procedures just described, other methods involve a more obvious use of coordination chemistry. These may find application in special systems. One approach is to use a soluble complex of silver halide as the source of silver halide and to precipitate the grains by diluting the complex-containing solutions in an aqueous or alcohol solution in the presence of gelatin, if desired. The silver halides can be dissolved at high concentrations in solvents such as dimethylformamide, pyridine or dimethylaniline. Pouring these solutions into an aqueous medium precipitates the silver halide grains.[8]

In a second procedure, useful for forming reversal or direct X-ray emulsions, a high concentration of ammonia is used to form a complex precipitate with silver bromide, by mixing ammoniacal silver nitrate and ammoniacal potassium bromide. Dilution with water decomposes the ammonia complex, and silver bromide grains form.[9]

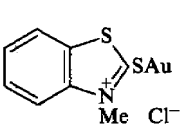
A light-insensitive photographic element consisting of incipient light-sensitive silver halide grains can be prepared by coating the light-insensitive complex $(NH_4)_2[AgBr_3]$ from an inert aprotic solvent such as methyl ethyl ketone. Areas of the film become light-sensitive AgBr when moistened with a protic solvent such as water or alcohol.[10]

In another process,[11] silver bromide is dissolved in a concentrated solution containing excess bromide salts, forming complex ions such as $[AgBr_3]^{2-}$ and $[AgBr_4]^{3-}$, and coated with a binder such as gelatin. Washing the coating with water dilutes bromide and precipitates silver bromide grains. In a variation, solutions of silver halide complex ions are diluted to produce silver halide grains in the absence of binder. The microcrystals can then be ripened, sensitized or otherwise modified in the absence of binder, and then mixed with binder just before coating.[12]

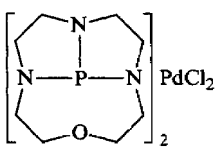
59.2.1.2 Chemical sensitization

The light sensitivity of silver halide emulsions can be greatly increased by chemically treating the grains in a process called chemical ripening, digestion, second ripening or afterripening. This is done after physical ripening and washing and usually involves a controlled heat treatment. Chemical agents that effectively increase emulsion light sensitivity include a number of metal salts and complex ions. The sensitizers are used in low concentrations, about 1×10^{-5} mole of sensitizer per mole of silver halide. The mechanism of action of these compounds is complex and not entirely understood. Again, James should be consulted as a good reference to the technical literature,[13] in addition to a recent review by Moisar.[14]

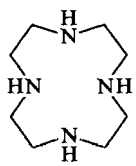
The most important sensitizers are salts and complexes of gold(I) or gold(III).[15–17] These can be used alone or in the presence of thiosulfate (itself a chemical sensitizer in very low concentration). The process is further complicated by interactions of gelatin with the added complexes or salts. Among the gold compounds commonly used are $Na[AuCl_4]$, $H[AuCl_4]$, $NH_4[Au(SCN)_2]$, $AuCl_3py$, $(AuCl_3)_2en$ and $Na_3[Au(S_2O_3)_2]$. These compounds with thiocyanate or thiosulfate ions can produce even larger sensitization effects (referred to as sulfur-plus-gold sensitization). Relatively insoluble gold compounds such as (**1**) may be used,[17] and water-soluble gold(I) thiolates such as $AuSCH_2CH_2CH_2SO_3Na$ have also been used.[18]



(1)



(2)



(3)

Complexes of other metals are used to sensitize emulsions, and some are used to sensitize even further (supersensitize) gold-sensitized emulsions.[19,20a] Among these are $(NH_4)_2[PtCl_4]$, $(NH_4)_2[PdCl_4]$, $(NH_4)_2[PdCl_6]$, $K_2[IrCl_6]$ and similar compounds with ruthenium and the other halides. Sensitization by iridium salts and complex ions has been reviewed recently.[20b] Mechanisms of action of palladium(II) salts and complex ions on gold-sensitized emulsions have been studied.[20c] Several phosphine complexes of palladium and platinum, for example (**2**), are reported to be effective sensitizers,[21] as are many macrocyclic polyamine compounds and their metal complexes,[22] for example the Cu^{II}, Ni^{II}, Fe^{III} and Rh^{III} chelates of the cyclen ligand, 1,4,7,10-tetraazacyclododecane (**3**).

Open-chain polyamines such as 1,4,8,11-tetraazaundecane and its complexes with Cu^{II}, Ni^{II} and Zn^{II} are chemical sensitizers as well,[23] although the effect of the chelates may be ascribable in part to their being a source of the free amine (a possible reduction sensitizer, another important class of chemical sensitizers).

Again, the precise roles of coordination-compound chemical sensitizers, in most cases, are not understood. In fact, their effects may have little to do with their own coordination chemistry. Many simple salts of gold and other noble metals are effective sensitizers. They also may be added to solutions during silver halide precipitation to produce 'doped' emulsions that have special properties. A variety of compounds that can act as ligands to metal ions are also effective alone as chemical sensitizers, the result of complicated oxidation–reduction, ion replacement and adsorption reactions on the silver halide grain surface. These include polyamines, phosphines and thioether- or thiol-containing compounds. The chemistry of these materials with the silver halide surface is discussed in the reference literature.

59.2.1.3 Emulsion stabilizers

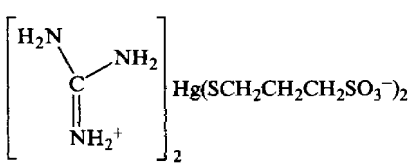
Stabilizers are agents that retard the formation of developable fog or the changes in other sensitometric characteristics of an emulsion that occur during storage, particularly at high temperatures or humidities. They are usually added to an emulsion after chemical sensitization, just before coating. In current usage, antifoggants or fog restrainers are defined as agents that, during

development, slow the rate of fog density growth to a greater extent than they slow image density growth. Earlier patents often use the terms 'antifoggant' and 'stabilizer' synonymously when referring to stabilization effects. Some technical aspects of antifoggants and stabilizers are discussed by James.[24]

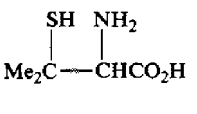
Numerous coordination compounds can be used as emulsion stabilizers, some of which, at lower concentrations in the chemical ripening process, also act as chemical sensitizers. Several transition metals are represented, including gold, silver, cobalt, rhodium, iridium, palladium, platinum, zinc, cadmium, mercury, rhenium and manganese. Stauffer and Smith reported that many rhenium, palladium and platinum complexes are good stabilizers, including $K_2[ReCl_6]$, $K_2[Pd(SCN)_4]$, $[Pd(en)_2]Cl_2$, $PdCl_2py_2$, $PdCl_2(NH_3)_2$ and $[Pt(NH_3)_4]Cl_2$.[25] Trivelli and Smith found that several ammonium salts of the chloro complex ions of $Pd^{II, IV}$, Pt^{II}, $Ir^{III, IV}$ and Rh^{III} are also effective.[26]

Gold complexes stabilize emulsions, particularly gold-sensitized ones. Such complexes include the previously mentioned $K[AuCl_4]$ and $AuCl_3py$ together with $K[Au(SCN)_4]$ and $AuCl_3SMe_2$.[27] Insoluble gold salts such as (**1**) also stabilize gold-sensitized emulsions.[28] The bis(thiosulfato)-aurate(I) complex, among others, stabilizes direct-positive emulsions against losses in maximum density when added to the emulsions after the fogging step.[29]

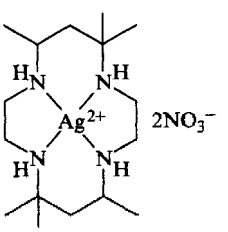
Many dithiocarbamate complexes of zinc, silver, cadmium or mercury improve emulsion stability, including bis(dibenzyldithiocarbamato)-zinc(II) or -cadmium(II) and silver(I) diethyldithiocarbamate.[30] Cadmium salts, mixed with citric acid or tartaric acid and added to the emulsion, are reported to be effective.[31] Mercury(II) complexes of ethylenediaminetetraacetic acid (EDTA) and related ligands[32] and of solubilized thiols such as (**4**) can be used.[33] Other coordination compounds reported include EDTA and related ligand complexes of Co^{II} and Mn^{II},[34] mixtures of Co^{II} salts with penicillamine[35] (**5**) and macrocyclic complexes[36] of Ag^{II} such as (**6**). The latter compounds may be used in diffusion transfer systems in which transferred maximum densities are stabilized.



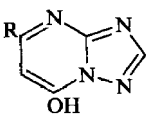
(4)



(5)



(6)



(7)

Several metals, including iron, copper and tin, can fog emulsions. Emulsions can be partly stabilized by sequestering these metallic species with suitable ligands. Catechol derivatives are reported to be helpful in preventing fog from this source. Examples include 1,2-dihydroxybenzene-4-sulfonic acid (sodium salt) and 1,2-dihydroxybenzene-3,5-disulfonic acid (disodium salt).[37]

Many organic compounds can stabilize emulsions. These compounds are more diverse in nature and greater in number than the coordination compounds mentioned here, and among them are stabilizers of the most practical and theoretical significance, the *s*-triazolo[1,5-*a*]pyrimidines.[38] The 7-hydroxy derivatives (**7**) are particularly useful, but the action of these compounds on emulsion grains is again complex, involving surface adsorption effects. For a discussion of mechanism, the paper by Cash and Ferguson and the references therein should be consulted.[38]

59.2.1.4 Developing agents and development modifiers

Developing agents reduce silver ions to silver metal. For an image to be formed, such compounds must be able to reduce exposed silver halide grains at a different rate (usually higher) than unexposed grains, and not all reducing agents that reduce silver(I) satisfy this criterion. See James[39] for a review of developing agents and their reactions.

A number of metal ions of variable valence, for example Fe^{II}, Ti^{III} and V^{II}, can reduce silver. Among the more significant coordination compounds are those of iron and titanium. Iron(II) ion, in the presence of fluoride or pyrophosphate to sequester the Fe^{III} formed, is a developer. The bis(oxalato)ferrate(II) ion, $[Fe(C_2O_4)_2]^{2-}$, is also a developer in the presence of excess oxalate.

The most important ferrous developers, however, are the complexes with ethylenediaminetetraacetic acid (EDTA) and related ligands, such as diethylenetriaminepentaacetic acid (DTPA), nitrilotriacetic acid (NTA) and *N*-hydroxyethylethylenediaminetriacetic acid (HETA). Complexes

with EDTA have received the most attention. Such developers can vary little in activity over a wide pH range (3–10).

Titanium(III) chloride in the presence of oxalate ions or complexed with other ligands such as EDTA, NTA, DTPA or HETA is a developer.[40] The Ti^{III}–DTPA developer maintains constant activity over a wide pH range (3–10), is relatively non-toxic and safe to handle, and has some desirable properties as a single-use developer.[41]

In contrast to using metal complex developers in solution, metal salt developer precursors such as CuNCS, $CoCO_3$, CoC_2O_4 or MnC_2O_4 can be incorporated directly into silver halide emulsion layers. After exposure, the emulsion is developed by immersion in an ethylenediamine or other amine solution, generating a complex ion developer *in situ*.[42]

Metal complex formation can be used to stabilize an otherwise reactive or unstable organic developer, such as hydroquinone or *p*-phenylenediamine, to permit its incorporation into silver halide emulsion layers or adjacent layers. For example, catechols and hydroquinones can be mixed with several metal salts of lead(II), cadmium or barium and incorporated into emulsion layers. Treating the film with an activator solution containing an anion that forms an insoluble salt of the metal ion (SO_4^{2-}, CO_3^{2-}) liberates the organic developer.[43] The structures of the complexes are not known. Similarly, complex associations of *p*-phenylenediamine developers with Cd, Cu^{II}, Pb^{II} or Zn salts can be used.[44]

Metal complex formation can be used to change (raise) the pH of a processing medium and thereby initiate development. A developer in solution that is unstable at the high pH of development can be kept stable at a lower pH. Treating an exposed emulsion layer with a solution containing the developer and a metal-complexing agent and then bringing the layer into contact with an active metal surface (*e.g.* Al, Zn) results in the dissolution of the metal and the generation of hydrogen and hydroxide ions. The pH of the medium is raised, and development can begin.[45] Examples of sequestering agents are alkali metal citrates, tartrates and salts of EDTA.

Development modifiers alter the rate of development (development accelerators or inhibitors) or may render silver halide grains developable. Certain complexes of ruthenium, in particular $[Ru(NH_3)_6]Cl_3$, are accelerators of development with hydroquinones and ascorbic acid.[46] Several complex ions of cobalt, for example $[Co(NH_3)_5OH_2]^{3+}$, $[CoCl(NH_3)_5]^{2+}$ and $[Co(en)_3]^{3+}$, are development accelerators.[47]

Nucleating agents are compounds that chemically 'fog' or expose silver halide grains, rendering such grains developable. They are typically used in reversal photographic processes. Certain tin(II) salt reducing agents chelated with aminopolymethylenephosphonic acid act as nucleating agents. A mixture of tin(II) chloride and, for example, 1-hydroxyethylidene-1,1-diphosphonic acid $[MeC(OH)(PO_3H)_2]$ forms a nucleating agent for reversal black-and-white or color processing.[48]

59.2.1.5 Bleaching and fixing agents

Most photographic processes require that certain operations be performed after the image formation step, for the image to be obtained in a suitable form. In simple black-and-white processes, the silver metal image is retained in the emulsion layer and undeveloped silver halide is converted to a soluble complex, which is washed out of the emulsion (fixing). In processes where an image in silver metal is used to obtain a secondary image (in dye, for example), it is often desirable to remove the silver metal by oxidizing it (bleaching) and then fixing it in the same (a bleach–fix process) or a subsequent processing step.

Many compounds and ions form silver ion complexes that are soluble with large enough stability constants to permit their use as fixing agents. A good fixing agent must satisfy other important conditions. It should be relatively inexpensive, non-toxic, non-odorous and stable at the pH of the processing bath. It should not react with image silver or dyes if present and should not attack the gelatin in the emulsion. If bleaching agents are also present, the fixing agent should not be oxidized by them at an unsuitable rate. A point of considerable importance is that the soluble silver complexes formed with the fixing agent should be stable under the more dilute solution conditions of subsequent washing operations. Otherwise, silver salts could reprecipitate in the emulsion layers.

A list of more common silver complexing agents includes thiosulfates, thiocyanates, sulfites, cyanides, ammonia and other amines, thiols, thiourea, thioacids, thioethers and alkali halides. Most are not practical as fixing agents because they fail to satisfy all the above criteria. Many find use as silver halide stabilizers (Section 59.2.1.8). These include thiocyanate, thiourea and other thioorganic compounds. These and other complexing agents such as cyclic imides, phosphines and arsines find use in silver halide diffusion transfer processes (Section 59.2.1.6).

The most practical fixing agent is sodium or ammonium thiosulfate.[49] It is inexpensive and readily purified, and forms stable, soluble complexes with silver ion, among them $[Ag(S_2O_3)_3]^{5-}$ and $[Ag(S_2O_3)_2]^{3-}$. The latter predominates in practical fixing baths. As silver ion concentration builds up in used fixing baths, polynuclear complexes such as $[Ag_2(S_2O_3)_3]^{4-}$ and $[Ag_3(S_2O_3)_4]^{5-}$ are formed. Thiosulfate, especially when stabilized with sulfite, is a useful fixing agent under basic, neutral and moderately acidic conditions. Since it is oxidized relatively easily, it cannot be used in the presence of strong bleaching agents (*e.g.* $[Fe(CN)_6]^{3-}$) unless the bleach–fix formulation is prepared a short time before use. Practical, stable bleach–fix processing solutions containing thiosulfate have milder oxidants such as ethylenediaminetetraacetatoferrate(III), $[FeEDTA]^-$ (*vide infra*).

Other compounds can be used as fixing agents in special circumstances. In the dye-bleach process (Section 59.2.2.2) an image in silver metal is used to reduce and destroy a dye, producing a reversal image in dye. The dye is reduced at low pH in the presence of an electron-transfer catalyst. Fixing agents such as thioureas are useful and stable under the acidic processing conditions.

The dye-bleach process can be carried out in a reversal mode. The initially formed silver image must be oxidized and removed, leaving a reversal image in undeveloped silver halide, which can then be developed and used to reduce and destroy a dye. Since the reversal image in silver halide must be left intact, bleaching agents that oxidize silver directly to soluble salts are sometimes used. These include $H_2SO_4/K_2Cr_2O_7$ and $H_2SO_4/KMnO_4$. These mixtures are highly corrosive, however, and may attack other components of the film such as gelatin or the image dyes. Milder oxidants can be used in the presence of suitable fixing agents for Ag^I that will not dissolve the imagewise-distributed silver halide in the film. Thus, $Fe(NO_3)_3$, $[Fe(CN)_6]^{3-}$ or $Cu(NO_3)_2$ can be used as bleaching agents in the presence of thioether-containing fixing agents such as $HO_2CCH_2SCH_2CO_2H$, $MeSCH_2CH_2OH$ or $HOCH_2CH_2SCH_2CH_2OH$, which will not attack the silver halide.[50]

A much older reversal process is based on the differential solubility of AgBr and AgCl in concentrated solutions of chloride ion. An AgBr emulsion is exposed and developed, and then the image silver is bleached back to AgCl with a chloride-containing bleach such as $CuCl_2$ or $[Fe(CN)_6]^{3-}$/NaCl. Washing the emulsion with saturated sodium chloride solution dissolves and removes the AgCl as $[AgCl_2]^-$, leaving the less soluble AgBr behind as a reversal image.[51]

Some fixing agents are sufficiently compatible with strong oxidizing agents to make good bleach–fix formulations. These include thioether compounds such as 2,5-dithiaoctanedioic acid, 3,6,9-trithiaundecandedioic acid and 3,6,9,12-tetrathiatetradecanedioic acid, which may be used with $[Fe(CN)_6]^{3-}$ bleaches.[52] Several dialkylaminoalkylthiols, such as diethylaminoethanethiol, function as bleach accelerators and fixing agents in persulfate-containing bleach–fix formulations.[53]

Other ligands reported to be useful fixing agents are ammonium mercaptoalkanesulfonate salts such as ammonium 3-mercaptopropanesulfonate[54] and several tertiary phosphines such as 3-aminopropyldimethylphosphine.[55] The latter promotes the bleaching of image silver by molecular oxygen or several organic oxidants.

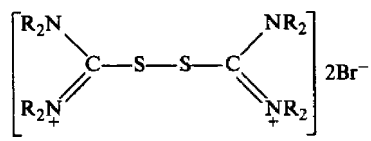
A wide variety of oxidants can be used for bleaching silver, and among the most important are the complexes hexacyanoferrate(III), $[Fe(CN)_6]^{3-}$, and ethylenediaminetetraacetatoferrate(III), $[FeEDTA]^-$. Ferricyanide is a relatively strong and rapid bleaching agent, generally used with a halide salt such as NaBr to rehalogenate or convert silver to silver bromide prior to a fixing step. Owing to its toxicity, it is being used less today than the environmentally more suitable ammonium ethylenediaminetetraacetatoferrate(III)/NH_4Br bleach formulation. Several other ligand systems for sequestering iron(III) produce bleaches, including a number of aminocarboxylate ligands related to EDTA and similar polymethylenephosphonic acid ligands such as $MeCH(OH)(PO_3H)_2$, $N(CH_2PO_3H)_3$ and $(HO_3PCH_2)_2NCH_2CH_2N(CH_2PO_3H)_2$.[56]

In bleach–fix formulations, most of which contain fixing agents such as ammonium thiosulfate or ammonium thiocyanate, mild oxidizing agents are used, in particular the chelates of Fe^{III}, Co^{III} or Cu^{II} with (ammonium) EDTA and related ligands.[57] A problem with the $[FeEDTA]^-$ formulations when color films and papers are processed is balancing pH, solubility and bleaching rates. At lower pH (~4) the bleach is most rapid but less soluble, and the ethylenediaminetetraacetatoferrate(II), as its concentration increases in used processing solutions, tends to partially reduce the cyan image dye of the film to a leuco form. This requires a subsequent oxidation to fully restore the image dye. At higher pH (~8), cyan dye reduction is less of a problem, bleach solubility increases, but bleach potency (thermodynamically and kinetically) is reduced. This is ascribable to the conversion of the $[FeEDTA]^-$ complex ion into a μ-oxo complex ion dimer. The dimerization

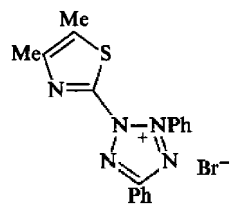
can be suppressed by adding a ligand for Fe^{III} such as excess SCN^-, F^- or thiourea to the bleach–fix bath, thereby improving the bleach activity.[58]

The components of a bleach–fix formulation can be applied to a photographic element other than from an aqueous processing bath. The $[FeEDTA]^-$ bleaching agent can be coated as a sheet together with a coatable fixing agent such as a thiourea or thioamide. Bleaching and fixing are effected by laminating the bleach–fix sheet to a photographic film.[59]

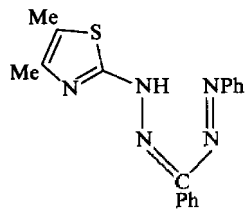
Other interesting bleach–fix formulations contain oxidizing agents that incorporate silver ligands or upon reduction become fixing or chelating agents for silver(I). For example, the disulfide compounds (**8**) derived from oxidized thioureas act as silver bleaching and fixing agents. They are used in the presence of an additional fixing agent such as thiourea or thiocyanate.[60] When it is desirable to replace partially or completely a silver image with a dye image, tetrazolium salts such as (**9**), which contain at least one ligand for metal ions, can bleach silver and in so doing generate an image in formazan dye (**10**) and complex the silver ions.[61] Suitable ligands are thiazoles, imidazoles and pyridines. The precise nature of the silver(I) complex is not established.



(**8**) R = H, Me



(**9**)



(**10**)

59.2.1.6 Silver halide diffusion transfer processes

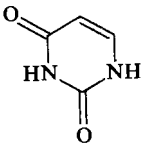
A negative image in exposed silver halide grains or developed silver is not the only image present in a conventional silver halide emulsion. A positive image exists in the unexposed grains, or the undeveloped grains, and this image can be used by transferring it from the light-sensitive element to some receiver material. The image is transferred by using a complexing agent, or silver 'solvent', to form soluble, diffusible complexes with silver halide. The complexes diffuse to a receiver element where they in turn are developed to produce an image. Although the processing steps of silver halide development, silver halide diffusion transfer and subsequent transferred image development could be separate steps, in practice the overall process is usually carried out with one processing solution in which all three steps occur simultaneously or in rapid succession. The receiver material for the transferred image can be, among other things, a reflective paper for a photographic print, a transparent sheet for projection material or the metal surface of a printing plate. Diffusion transfer processes have many diverse and important applications, because of the various receivers that can be used and the various imaging or dye-forming chemistries that can be linked to the transferred image.[62] James[63] gives a technical discussion of the process.

Coordination chemistry is at the heart of the silver halide diffusion transfer process, and many types of compounds are silver solvents for the process. Good solvents are, at first glance, good fixing agents in that they complex and solubilize silver halide, and the complexes can diffuse out of the emulsion layer. However, the concentrations at which the solvents are used are usually less than if they were to be used simply as fixing agents. At too high concentrations, halide will be dissolved too fast relative to concurrent silver development, and high concentrations of solvent will retard the development of the transferred image in the receiving layer, owing to excessively low silver ion activity. Diffusion transfer processing formulations consist of carefully controlled amounts of developing agent, silver solvent and other process control agents.

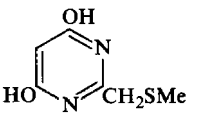
In practical systems, no solvent is as universally effective as sodium thiosulfate, $Na_2S_2O_3$. It is inexpensive, stable and produces few undesirable side effects such as stains, odors or toxicity. It rapidly forms stable, soluble complex ions with silver halide (for example $[Ag(S_2O_3)_2]^{3-}$), which are rapidly diffusible. Several other silver complexing agents are proposed as being useful in diffusion transfer processes, however, and some of these are used either singly or in combination with other, more common solvents. Some are used with certain developers.

A number of cyclic imides, such as uracil (**11**), can be used in conjunction with a nitrogenous base.[64] These compounds are added to hydroxylamine developer formulations. Several thioether-substituted 2,4- or 4,6-dihydroxypyrimidines, such as (**12**), are useful.[65] Thioether-containing carboxylic acids can be used in the preparation of electrically conducting transferred silver images. These include 3-thiapentanoic acid, 3-thiapentanedioic acid and 3,6-dithiaoctanedioic acid.[66] Mercaptobenzoic acids are used alone or with a cyclic imide solvent to produce lithographic

printing plates.[67] Several thioether-substituted ethylenediamines such as (**13**) are reported to be good solvents,[68] and crown ethers (**14**) derived from such acyclic thioethers also are silver solvents.[69]



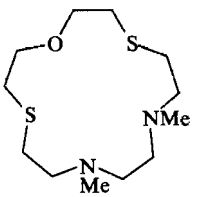
(**11**)



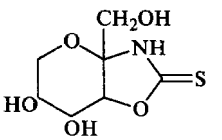
(**12**)

$HOCH_2CH_2SCH_2CH_2N(Me)CH_2CH_2N(Me)CH_2CH_2SCH_2CH_2OH$

(**13**)



(**14**)



(**15**)

Other sulfur-containing complexing agents are silver solvents under acidic and neutral conditions as well as at high pH. These include the thiosemicarbazones of several sugars, such as glucose, or of dihydroxyacetone.[70] The reaction of thiocyanic acid with any of several sugars produces a 2-oxazolidinethione such as (**15**), which functions as a solvent in alkaline conditions.[71]

Numerous alkyl and aryl phosphine, arsine and stibine compounds are described as being silver solvents. Examples are tris(*p*-hydroxyphenyl)phosphine and bis(2-carboxyethyl)methylphosphine.[72]

59.2.1.7 Silver image stabilization

Although properly fixed and washed images in silver metal are very stable compared to most images in organic dyes, silver images are much more susceptible to corrosion by atmospheric components (oxygen, sulfur compounds) when silver(I) complexing agents remain in the image-containing element. This is the case with many silver diffusion transfer systems, monobath processing systems (in which development and fixing take place with the same processing solution) and other rapid wet or dry processing systems in which the fixing agent may not be washed completely out of the image areas or may be deliberately left in the film. Many organic compounds, including a large number of aromatic and heterocyclic thiol or thione compounds, when included in developing formulations or subsequent processing solutions, are helpful in retarding this silver corrosion or bleaching, probably because their adsorption to the silver surface renders it unreactive.

A few transition metal complexes can also be used to stabilize a silver image. These are used in diffusion transfer systems. Compounds of gold(I) with 2-mercaptobenzimidazole, for example, can be incorporated into the silver halide emulsion layer. The compounds, or components from them, are sufficiently mobile under processing conditions to stabilize the transferred silver image toward environmental bleaching.[73] More recently, stabilization effects have been reported for gold(I) compounds such as $AuSCH_2CO_2Me$, which hydrolyze under the processing conditions and become diffusible, together with the transferred silver halide.[74] They are essentially non-diffusible before hydrolysis. Their location and time of availability in films can thereby be controlled.

59.2.1.8 Stabilization of silver halide

Several imaging processes are designed to be compact and rapid. These include not only wet development processes but also dry photothermographic or thermographic processes. In such systems the light-sensitive material, often silver halide, is not washed from the film but remains in it and must be stabilized to light and storage conditions. A good stabilizing agent forms a complex with silver(I) that is light insensitive, colorless, non-crystalline and preferably of the same refractive index as the medium containing it. The stabilizing agent and its complexes should be non-toxic, odorless and non-deliquescent. The agent should not promote the corrosive bleaching of the silver metal image. Most useful stabilizing agents offer a compromise in satisfying these performance criteria. James[75] gives a general discussion of stabilizing agents.

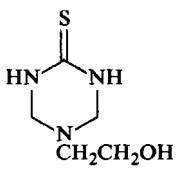
At first glance, good fixing agents should be good stabilizers. However, a good fixing agent needs merely to dissolve silver halide rapidly and promote its rapid washing from the film. Thiosulfate

performs this task admirably, keeping Ag(I) in solution even as the washing produces increasingly dilute solutions. As a stabilizing agent, however, thiosulfate is less than satisfactory. It usually leaves powdery residues on emulsion surfaces, which can cause stains, and tends to promote the aerial bleaching of silver images.

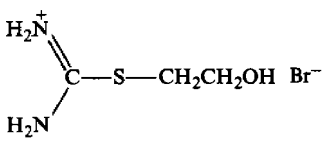
The best stabilizers are thiocyanate salts and thioureas. Other mercapto compounds such as mercaptoacetic acid, thiosalicylic acid and cysteine [$HSCH_2CH(NH_2)CO_2H$] can be used. Thioureas form stable complexes with silver(I) but can produce staining deposits of Ag_2S if the photographic material becomes alkaline. They can also promote the aerial bleaching of silver images, and they soften gelatin, resulting in tacky films. A derivative (**16**) of thiourea is reported to be an effective stabilizer and fixing agent, its use resulting in non-sticky films.[76]

The most widely used stabilization agents are thiocyanate salts. Thiocyanate forms stable salts (AgSCN) and complex ions ($[Ag(SCN)_2]^-$) with silver(I) that are light stable and under alkaline conditions do not generate Ag_2S. However, thiocyanate often makes gelatin films tacky (partly owing to reactions with gelatin and partly owing to deliquescence), and silver images are subject to bleaching. Silver surface passivating agents often need to be used to stabilize silver images in the presence of thiocyanate.

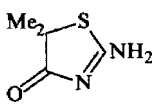
Several other stabilizing agents or precursors thereof are useful in special applications. Isothiouronium compounds[77,78] such as (**17**) and thiazoline compounds such as (**18**) can be incorporated into films, where they are inactive under acidic or neutral conditions. They generate active fixing and stabilizing agents under basic conditions. Metal salts of *N*-substituted aminoalkylthiols (**19**) are non-volatile, non-crystalline fixing and stabilization agents, which are active under neutral conditions.[79]



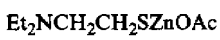
(**16**)



(**17**)

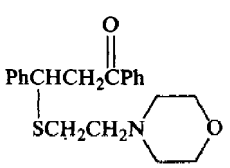


(**18**)

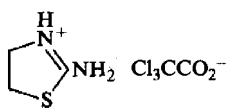


(**19**)

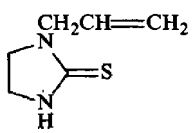
Many compounds can be converted by heat into active stabilization agents and thus find use in photothermographic or thermographic elements. These precursor compounds can be incorporated directly into the imaging elements. Examples include the isothiouronium salt (**17**)[80] and thiol adducts of chalcones such as (**20**),[80] the 2-amino-2-thiazolinium carboxylate (**21**),[81] the imidazolidine-2-thione (**22**),[82] the *N*-substituted 1-phenyl-5-mercaptotetrazole (**23**)[83] and the *S*-alkylated 1,2,4-triazolium-3-thiolate (**24**).[84] Several triarylphosphine and triarylphosphorane stabilizer precursors, such as (**25**), are described as useful sources of stabilizing agents in heat-stabilizable systems.[85]



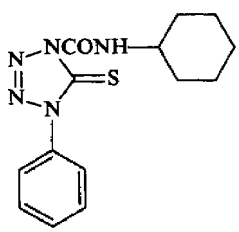
(**20**)



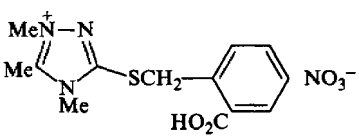
(**21**)



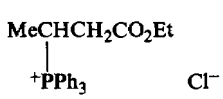
(**22**)



(**23**)



(**24**)



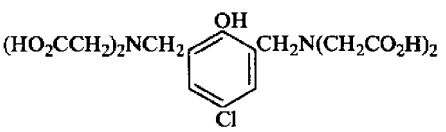
(**25**)

59.2.1.9 Antistain agents

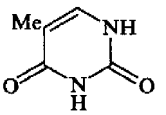
If photographic materials are processed by developing solutions containing heavy metal ions, in particular iron(III) or copper ions, stains often occur. The addition of an inositolpolyphosphoric acid to a color-developing solution complexes iron(III) ion, thereby preventing stain.[86] In addition, aerial fog caused by heavy-metal ion catalyzed oxidation of the *p*-phenylenediamine color devel-

oper is diminished. The use of other complexing agents such as the iminodiacetic acid derivative (**26**) has been disclosed for the same purpose.[87] These compounds are reported to be more effective than EDTA.

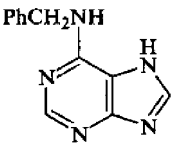
In dye-developer transfer processes the use of a silver halide solvent or complexing agent such as sodium thiosulfate is effective in increasing film speed. However, this may result in the transfer of a silver-containing species to the image-receiving or viewing layer, where on exposure to light it is reduced to metallic silver, which darkens the print. A silver halide complexing agent such as 5-methyluracil (**27**) used in place of the thiosulfate together with 6-benzylaminopurine (**28**) gives the desirable photographic speed effect, while preventing the photolysis.[88]



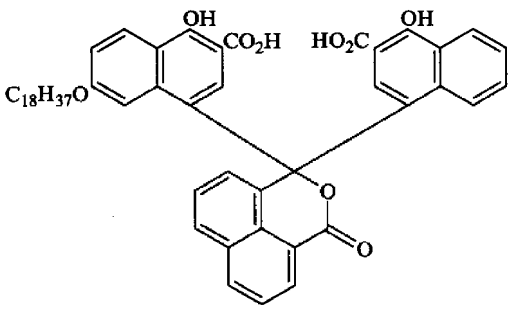
(**26**)



(**27**)



(**28**)



(**29**)

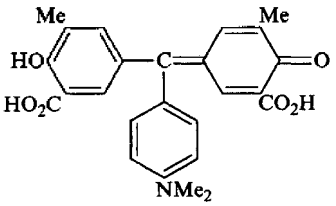
In diffusion transfer processes such as in the Polaroid SX-70 dye-developer film, where the dye image is viewed against a background of titanium dioxide, a print can yellow during storage.[89] The nature of this yellowing is not fully understood, but it can be partially controlled by including EDTA in the processing composition. One possible explanation is that titanium ions form a yellow complex with the phthalein optical filter agent (**29**), which contains salicylic acid functions in the molecule. EDTA presumably preferentially complexes the titanium ions. Complete control by EDTA is not possible, which suggests that there may be more than one source of the yellow stain.

59.2.2 Dyes and Imaging Chemistry

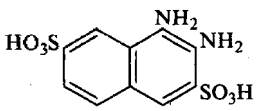
59.2.2.1 Filter dyes

Filter dyes are used in photographic systems for several reasons. They are used to prevent the unwanted response of spectrally sensitized silver halide. For example, the red layer may be sensitive to green as well as red light, and a filter has to be used to absorb the green light to prevent incorrect exposures. Also, the sharpness of photographic images can be impaired by light scattering due to the silver halide grains in the light-sensitive layers. The harmful effect of this scattering can be minimized by dyeing the gelatin in the photosensitive layers with dyes that absorb in the same spectral region to which the emulsion is sensitive. Sharpness problems are also caused by reflections off the film base, and antihalation dyes are coated beneath the photosensitive layers to prevent these.

Dyes for these particular applications need to have special properties: they should not wander from layer to layer and they should be capable of being removed or destroyed during the photographic processing. The aluminum chelate of the fuchsone dye (**30**) exhibits these properties, *i.e.* it is not washed out of a gelatin coating at pH 7, but the color is discharged by an alkaline developer solution and it is suitable for use as an absorbing dye for the green region.[90] In combination with other dyes it can also be used for antihalation.[91] The iron complex salts of 1,2-diaminonaphthalene-3,7-disulfonic acid (**31**) absorb red light and can be used for antihalation.[92] These dyes improve the sharpness of the red layer but have the disadvantage that they are mobile. Sulfonic acid substituted copper phthalocyanine derivatives[93] have also been used to improve red-layer sharpness.



(30)

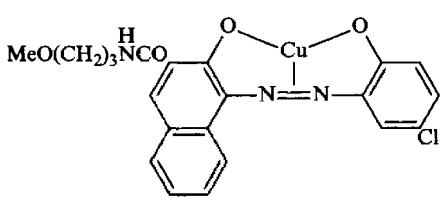


(31)

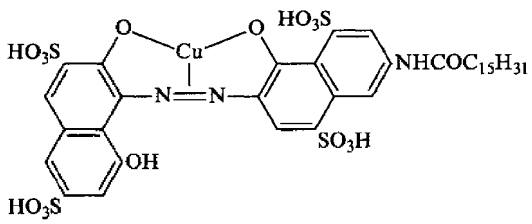
59.2.2.2 Silver dye-bleach process

The silver dye-bleach process depends on destruction of a dye in a photographic layer in an amount proportional to the quantity of image silver present.[94,95] The dye is normally an azo dye in which the azo bond is cleaved. Over the years a variety of metal-complexed azo dyes have been described for use in this process. These dyes must be immobile: they must not wander from layer to layer, or color contamination of the final image will result. However, they must be reactive enough in an aqueous environment for the azo bond to break.

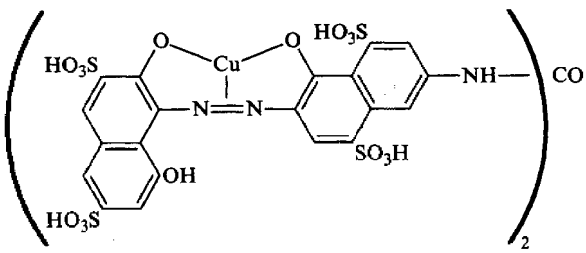
The combination of these properties can be accomplished in different ways. One method is to ball mill the water-insoluble metal-complexed dye such as (**32**) to a fine particle size and then disperse it in gelatin.[96] The resulting dispersion is reactive enough to be reduced during the acidic bleaching step without the unreduced dye being mobile. Another option is to use a dye with several water-solubilizing groups and a hydrophobic moiety.[97] A suitable dye would be (**33**), which absorbs in the red. Alternatively, two of these chromophores can be linked, forming a molecule like (**34**) that is too large to migrate out of its own layer, but where the azo bond can still break.[98] Most complexes described as being useful in this process are derived from copper, although some chromium and nickel complexes are also disclosed.



(32)



(33)

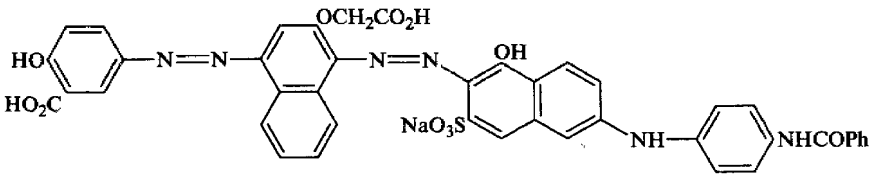


(34)

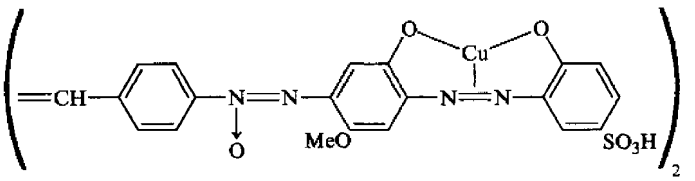
In another application the dyes used in the dye-bleach process are not premetallized; however, they contain metallizable sites so that after the bleaching step an after-bath treatment with a transition metal solution yields the metal-complexed dye. Bisazo dyes such as (**35**) yield greenish blue images after processing and treatment with a copper or nickel acetate solution.[99] Complexation can and presumably does occur at more than one site in the molecule.

A black-and-white system based on the silver dye-bleach process contains the single azoxy copper-complexed dye (**36**).[100] During bleaching, low pH solutions are used and the dye is partially demetallized. This necessitates an after-bath treatment with a copper-containing solution. Dyes other than those containing the azo group can also be bleached, and derivatives of sulfonated copper phthalocyanine have been used to form cyan images.[101]

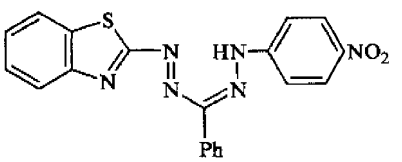
Formazans or their precursors, tetrazolium salts, have been used in dye-bleach systems. Certain formazans[102] such as (**37**) can complex with metal ions to give dye images with improved light stability.



(35)



(36)



(37)

59.2.2.3 Metallized dyes in diffusion transfer systems

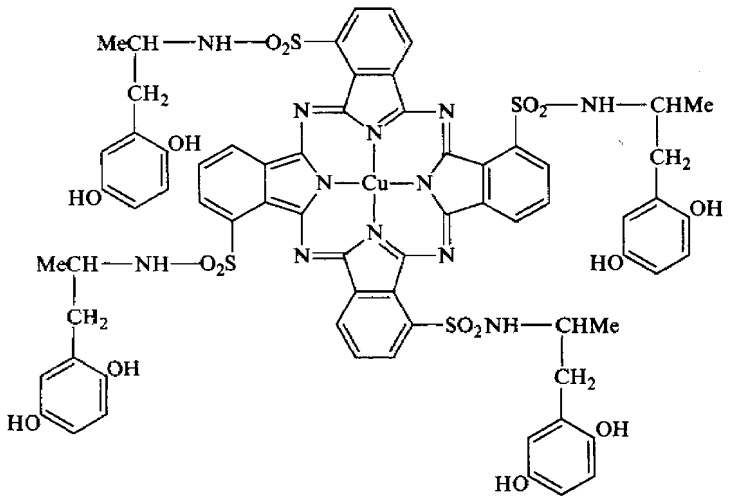
Azo dyes with ionizable groups, or substituents with an unshared pair of electrons, next to the azo linkage form complexes with transition metals.[103] Many such complexes have been described, and many have been used as fabric dyes because of their superior light stability.[104]

However, it was not until the advent of the Polaroid SX-70 diffusion transfer system of color photography using the dye-developer concept with preformed dyes[105] (in contrast to conventional color photography, where the dyes are formed during development) that it became possible to consider using metallized dyes to improve the light stability of instant color photographs. A subtractive color photographic process requires three dyes, yellow, magenta and cyan, to control the blue, green and red regions of the spectrum, respectively. Ideal image dyes should have low unwanted absorption in regions of the spectrum other than the ones they control. The curve shapes of many metallized dyes do not meet this requirement, thereby providing a major challenge to the dye chemist to design molecules with the right absorption properties. This task is made more difficult by the other requirements of the photographic system, such as the necessary base solubility and stability properties.

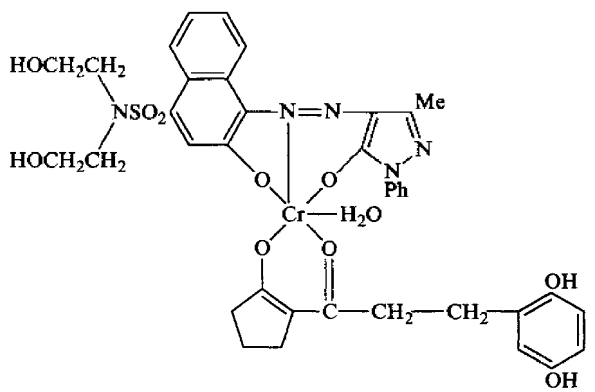
The dyes in the original Polaroid SX-70 film consist of one copper and two chromium complexes. The cyan dye developer (**38**) is based on copper phthalocyanine. The magenta dye developer (**39**) is a tridentate azo dye complexed with chromium(III), and the charge requirements for a neutral complex, together with the need for the presence of a hydroquinone moiety, are met in the following manner. A β-diketone with a hydroquinone residue attached is used as a second ligand to satisfy both requirements. The chromium is substitutionally inert, and the dye developer survives the high pH processing conditions intact. The yellow dye developer (**40**) contains a tridentate azamethine chromophore attached to the developer through the chromium in the same manner as the magenta. Light stability measurements[106] on Polaroid SX-70 film under a variety of conditions showed it to be more stable than conventional color prints in 1974.

A hexadentate chromium-complexed magenta dye (**41**) is described as being useful in image transfer applications.[107] It is prepared by attaching an iminodiacetic acid residue to an *o,o*-dihydroxyazo dye in an appropriate position so that it is suitably disposed to coordinate to the chromium.

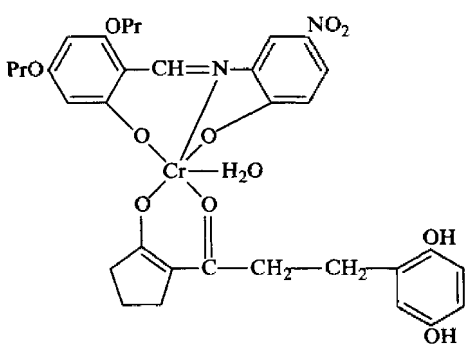
The foregoing discussion has concerned dyes in which the metal is already present before the photographic process is initiated. However, an alternative way of making use of the superior light stability of metallized dyes consists in metallization after the photographic process. Dye developers



(38)



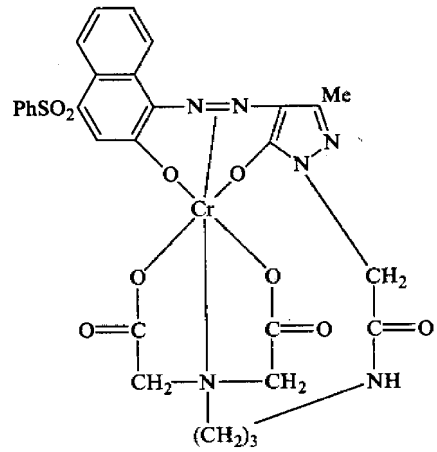
(39)



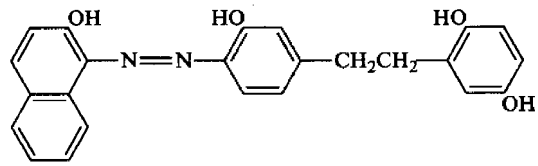
(40)

in which the dyes contain ligating groups can be metallized either by a post treatment with a copper-containing solution or by the incorporation of a copper chelate, *e.g.* $Cu(acac)_2$, in the receiver.[108] A typical example is the 2-naphthol dye (**42**). A different type of diffusion transfer color imaging is used in Kodamatic instant color film. Here a dye is released from an immobile species as a function of photographic development.[109] This is in contrast to the Polaroid film, where dye is immobilized as a function of development. Consider the sulfonamidonaphthol (**43**) shown in Scheme 1. In areas where silver development occurs, oxidation to the quinone imide (**44**) takes place, followed by deamidation under the high pH conditions to release the dye (**45**) as the sulfonamide. Numerous tridentate metallizable dyes have been disclosed for use in this type of system.[110] Obviously, only metal ions that react fast enough with the dye can be used. Cu^{II} and Ni^{II} are suitable, but Cr^{III} is kinetically too inert. The dyes can be divided into two types: those with monoanionic and those with dianionic ligating groups.

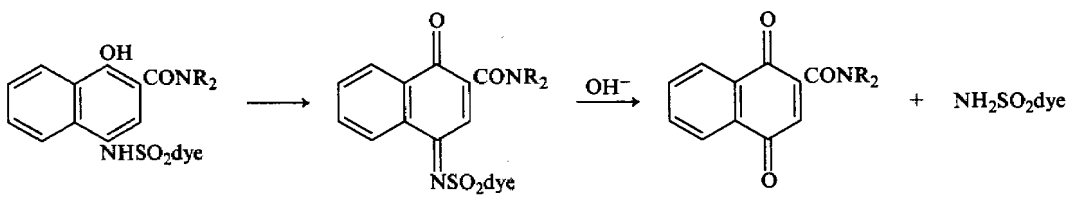
The pyrazolone (**46**)[111] and the cyanoketone (**47**)[112] are yellow monoanionic dyes when complexed with Ni, and the quinolinol (**48**)[113] and the naphthol (**49**)[114] are magenta. The pyridinol



(41)

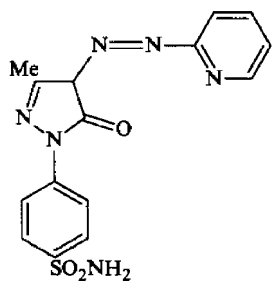


(42)

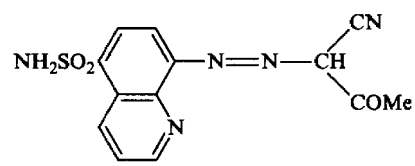


(43) (44) (45)

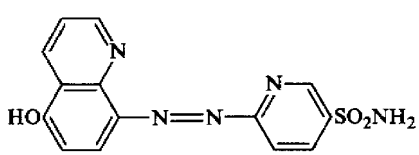
Scheme 1



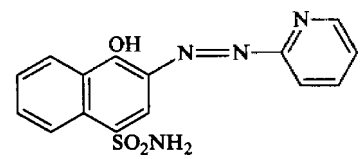
(46)



(47)



(48)

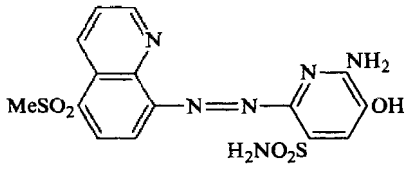


(49)

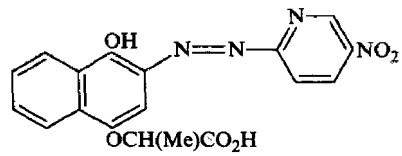
(**50**)[115] and the naphthol (**51**)[116] are monoanionic cyan dyes. The monoanionic pyridylazoaniline dye (**52**)[117] yields a black image when released and diffused to a nickel-containing mordant.

Examples of dianionic dyes are the yellow cyanoketone (**53**),[118] the magenta pyridinol (**54**)[119] and the cyan isoquinolinol (**55**).[120]

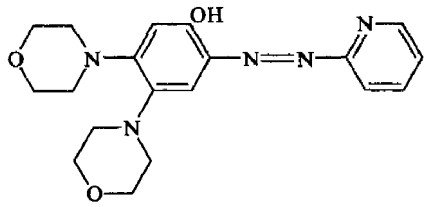
Some recent patents by Konishiroku refer to metallizable dyes of the dianionic type, with carboxyl groups as one of the ligands. A yellow pyridone (**56**)[121] and a magenta naphthol dye (**57**)[122] are two examples. Patents assigned to Agfa-Gevaert describe cyan metallizable dyes[123] from imidazo[1,5-*a*]pyridine such as (**58**) and yellow dyes[124] from ethyl acetoacetate such as (**59**). A Fuji patent[125] discloses a dye-releasing compound in which the dye is initially complexed with a metal



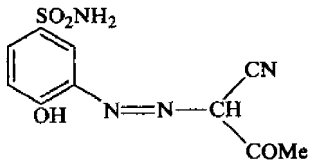
(50)



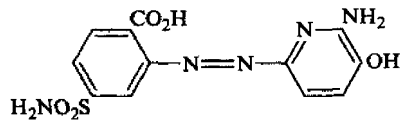
(51)



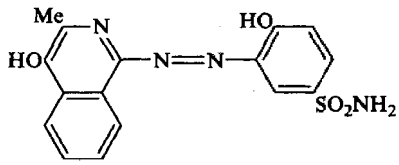
(52)



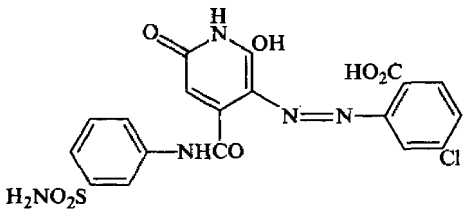
(53)



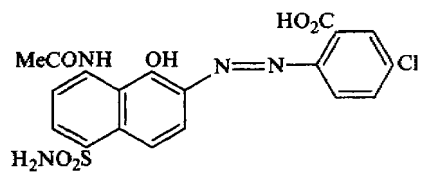
(54)



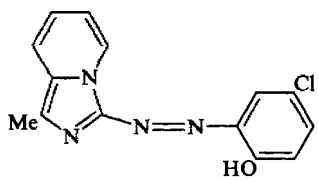
(55)



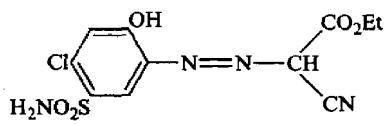
(56)



(57)



(58)

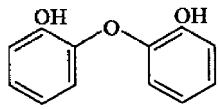


(59)

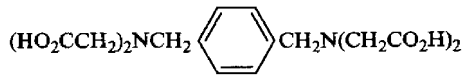
such as Zn^{II}. On transfer to the receiving layer, exchange takes place with the Cu^{II} or Ni^{II} present in the mordant.

For the operation of a metallizable-dye image transfer system, the metal ion must remain in place in the mordant receiver layer, and polymers that can complex metal ions have been described.[126,127] A typical one is based on poly(*N*-vinylimidazole).

In other methods of metallizing dyes in the receiver, metal chelates are used in a polymeric matrix. Examples of ligands for the metal ion include diazabicyclo[2.2.2]octane,[128] the 2,2′-bisphenol (**60**)[129] and the iminodiacetic acid (**61**).[130]



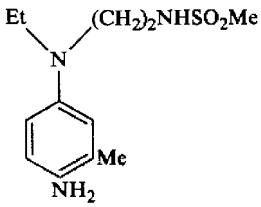
(60)



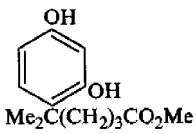
(61)

59.2.2.4 Other metallized dyes

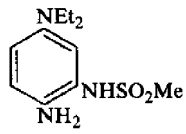
Modified conventional azamethine photographic dyes can be metallized after processing to give shifted hues and improved light stability. The dye formed from the developer (**62**) and the coupler (**63**) gives a blue image, which after treatment with $FeSO_4$ changes to brownish black.[131] In another example, the dye from the phenylenediamine (**64**) and the oxazolone coupler (**65**) is yellow, but on metallization with $CoSO_4$ it changes to black.[132]



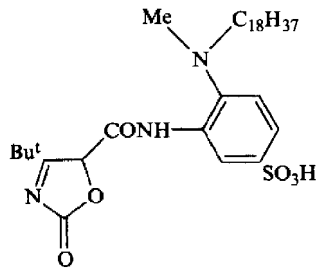
(62)



(63)

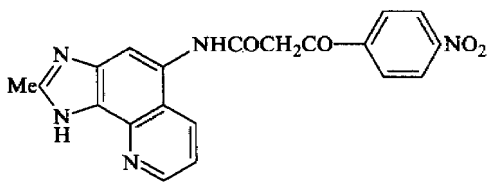


(64)

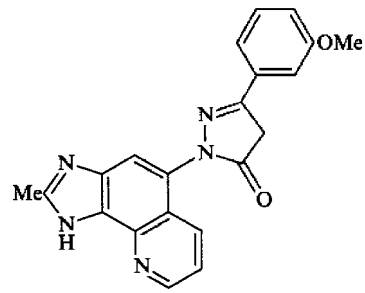


(65)

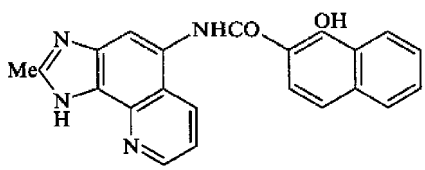
In other types of metallizable conventional dyes, the chelating site is not part of the chromophore, and thus there is not a large hue shift on metallization. In the yellow (**66**),[133] magenta (**67**)[134] and cyan (**68**)[135] couplers the metallizable site is the 1*H*-imidazo[4,5-*h*]quinoline substituent. This allows the option for metallization before or after the generation of the azamethine dyes by reaction with oxidized *p*-phenylenediamine. Advantages of improved light stability and acid fastness are reported for the metallized dyes.



(66)



(67)

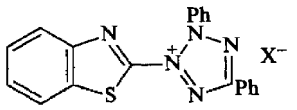


(68)

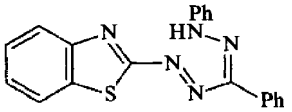
After development has taken place in a layer containing silver halide, two images are present: a negative one in metallic silver and a positive one in silver halide. The silver halide can be converted to a silver salt of a thiobarbituric acid, which is less soluble than the silver halide. Nitrosation of this insoluble silver salt produces an α-oximino ketone, which when treated with iron(II) ion yields a positive image in blue-green iron chelate.[136]

In another method of forming a colored image corresponding to undeveloped silver halide, the film is treated with a solution of $K_2[Ni(CN)_4]$. Nickel ion is thereby liberated imagewise and is captured by an organic complexing agent that is uniformly coated in the layer.[137] By the proper selection of the complexing agent, cyan, magenta and yellow dyes can be formed. For example, cyclohexanedione dioxime gives a magenta dye. Other transition metals can also be used.

The conversion of tetrazolium salts to metallizable formazan dyes on reduction has been utilized to form dye images.[138] For example, a silver image, when treated with a processing solution containing a tetrazolium salt such as (**69**) and sodium thiosulfate, is bleached and fixed, and the corresponding formazan dye (**70**) is generated in proportion to the silver metal. The dye image can then be treated with a transition metal ion to improve light stability or change the hue.



(69)

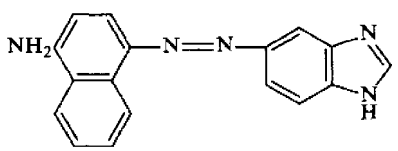


(70)

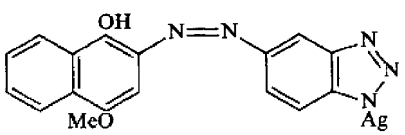
59.2.2.5 Metallized imaging compounds

Coordination chemistry can play a central role in diffusion transfer imaging chemistries, and reactions of coordination compounds control the diffusion of image-providing compounds in several image transfer systems. Of course, silver halide diffusion transfer has already been discussed in which a silver halide 'solvent' enables the diffusion of undeveloped silver halide to a receiver, where it is developed into an image.

The silver ions in the undeveloped portion of the photographic element can be used in other ways to control imagewise transfer of a color-providing substance to a receiver. In one system, color-providing compounds that are normally diffusible become non-diffusible when they react with silver complexes in the undeveloped portions of the film. A negative transferred image results, and a positive image remains in the photosensitive layer. For example, a compound such as (**71**) can be used, in which a dye and a species capable of forming an insoluble complex with silver ions are present.[139] (The developer contains a silver solvent formulation of sodium thiosulfate and sodium sulfite.) The incorporation of the silver salts of such compounds (for example **72**) into a photographic element can produce the same effect.[140] Where silver is developed the dye is liberated and diffuses to the receiver. In undeveloped areas it remains immobile.

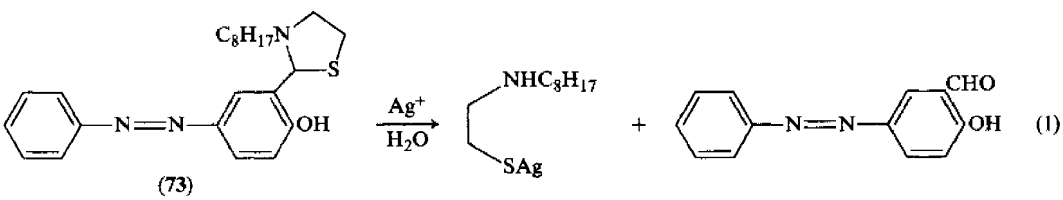


(71)



(72)

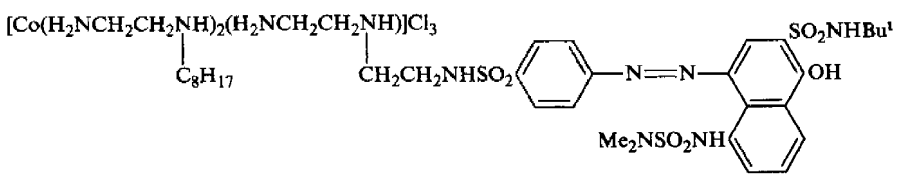
In another system, a non-diffusible compound reacts with undeveloped silver ions to liberate a diffusible dye, producing a positive transferred image.[141] Again, thiosulfate-containing developers are used. In this system, the silver ions catalyze the ring-opening hydrolysis of a thiazolidine (**73**), shown in equation (1).



(73)

(1)

Another non-diffusible dye-releasing compound (**74**) is an example of a number of substitution inert Co^{III} complexes in which the cobalt ion holds together long-chain alkyl ballasting groups and diffusible image dyes.[142] When these compounds are reduced by an imagewise distribution of a reducing agent, the labile Co^{II} complex formed releases a diffusible dye with the ethylenediamine ligand to produce a positive transferred image.

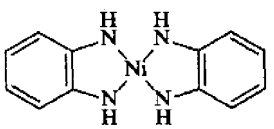


(74)

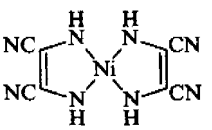
59.2.2.6 Image dye stabilization

Photographic image dyes can be stabilized to light by formation of metal complexes in certain cases (see Section 59.2.2.3). Also, some non-metallizable image dyes (azo, indoaniline, indophenol and azamethine dyes, to name a few) show improved resistance to light fading when in the presence of certain metal complexes in the photographic element. Many types of complexes are effective, and several metals are used, including Ni^{II}, Cu^{II}, Co^{II}, Pd and Pt.

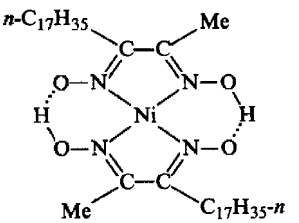
Fuji recently reported many complex compounds for use as light stabilizers for dyes. Examples discussed in the patents and shown here are generally Ni^{II} complexes. These include complexes of *o*-phenylenediamine (**75**),[143] (*Z*)-1,2-diamino-1,2-dicyanoethylenes (**76**),[144] dialkylglyoximes (**77**),[145] β-thioketoenolates (**78**),[146] *O,O*-dialkyl dithiophosphates (**79**),[147] 1,1-dithioalkenes (**80**),[148] and tetrathiotungstate(VI) complexes (**81**).[149] Also mentioned are complexes of *o*-aminobenzenethiols (**82**),[150] 2-heteroarylthiocarbonamides (**83**)[151] and various other sulfur- and nitrogen-containing bidentate, tridentate and tetradentate ligands, such as (**84**),[152] (**85**)[153] and (**86**).[154] Aldimine and ketoxime ligands (**87**) are also described.[155] These are treated with a metal salt solution in a final processing bath. Others report that 1,2-dithioalkene complexes such as (**88**) are useful image-dye stabilizers.[156]



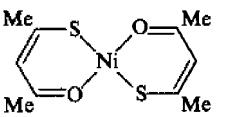
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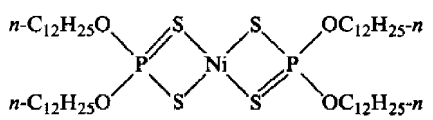
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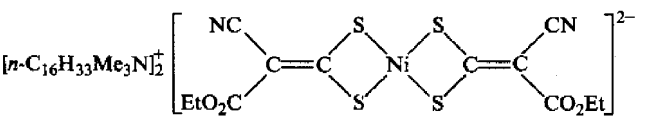
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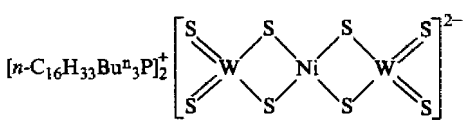
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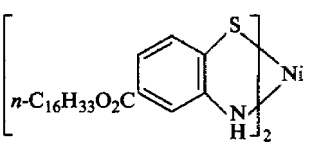
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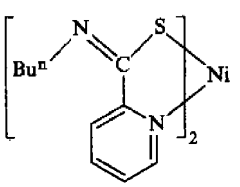
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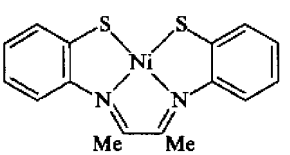
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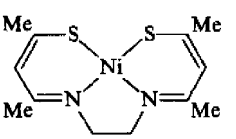
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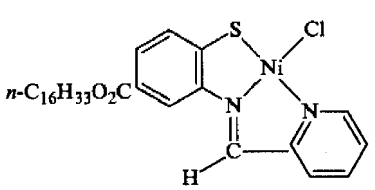
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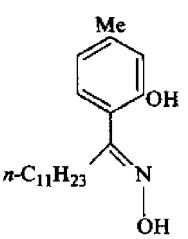
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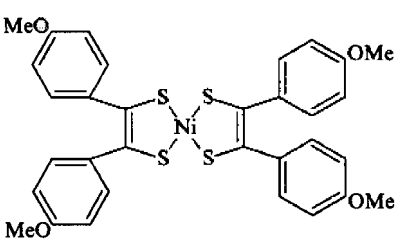
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(87)



(88)

59.3 PHYSICAL DEVELOPMENT AND OTHER IMAGE AMPLIFICATION SYSTEMS

In conventional silver halide photography the light-sensitive element is the chemically and spectrally sensitized silver halide crystal, which stores the latent image after exposure. The oxidizing equivalents used to amplify the latent image come from the remaining silver ions in the crystal. Alternative imaging systems have been devised in which the light-sensitive component is an organic or inorganic compound capable of forming an imaging catalyst or catalyst precursor (latent image) upon exposure to light. These systems find use where the expense of silver halide would be excessive or where the sensitivity (speed) of silver halide is not needed. Alternative image amplification chemistries have also been devised, largely to permit the use of less silver or materials less expensive than silver.

Solution processes in which a latent image is amplified into a visible image of a relatively inert metal deposit, the source of which is a soluble metal salt or complex, are called physical development processes. The physical development bath consists of a thermodynamically unstable mixture of a reducing agent (developer) and a soluble complex of the metal. The bath is formulated so that in the absence of latent-image catalytic sites or 'nuclei' the reductive deposition of metal is slow. Rapid deposition occurs in the presence of nuclei or latent-image catalytic sites.

Latent images or faint images in silver metal or other materials can be amplified by redox chemistries other than metal deposition. Several dye-forming redox chemistries have been discovered in which metal complexes serve as catalysts, catalyst precursors or one of the redox partners. The applications of coordination compounds in physical development and image amplification systems are therefore quite broad and diverse.

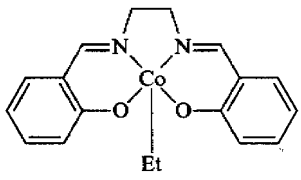
59.3.1 Photosensitive Materials

Silver halide grains are used as the light-sensitive component in many solution processes involving physical development. The latent images or partially developed latent images comprise the nuclei upon which the physical development reactions are catalyzed. There are many other nuclei-forming compounds, however, which find use in systems where the speed of silver halide is not required, its expense is unsuitable, or a more efficient catalyst for the physical development reaction is desired.

A number of palladium complexes form Pd^0 nuclei when struck by light, and the reactions catalyzed by such nuclei are diverse. Compounds such as $K_2[Pd(C_2O_4)_2]$ can be imbibed into a coating of (or coated in) a suitable polymeric binder. The nuclei formed upon exposure can catalyze the deposition of a metal such as nickel from a physical developer[157] or they can catalyze an amplification reaction in which hydrogen peroxide is decomposed and developing agents are oxidized, leading to dye formation.[158] Nuclei derived from this complex or from compounds such as $K_2[PdCl_4]$ or $[Pd(NH_3)_4]Cl_2$ catalyze the deposition of copper, cobalt, chromium, iron and nickel from stable physical developers. The deposition is not effectively catalyzed by silver latent images or nuclei.[159] Palladium nuclei catalyze amplification processes in which developers are oxidized by various Co^{3+} complexes (Section 59.3.3.2).[160] Other light-sensitive palladium complexes include $[PdXEt_2NCH_2CH_2NHCH_2CH_2NEt_2]BPh_4$ (X = Cl, SCN, N_3). The nuclei catalyze the reduction of tetrazolium salts to formazan dyes by formaldehyde, NaH_2PO_2 or borane reducing agents or the reduction of leucophthalocyanine dyes to phthalocyanine dyes.[161]

Several copper(I) and copper(II) complexes form nuclei for the catalytic deposition of copper or nickel. These include phosphite complexes[162] of Cu^I such as $CuP(OMe)_3BH_3CN$ or $[Cu(P(OMe)_3)_4]BPh_4$ and Cu^{II} amine complexes[163] such as $[Cu(en)_2][BPh_4]_2$ or $[Cu(bipy)_2][BPh_4]_2$. The complexes are only ultraviolet sensitive, permitting their being handled in daylight. They are considered useful in printed circuit manufacturing.

Cobalt complexes can be used as light-sensitive elements in a number of imaging processes, perhaps most notably in photothermographic systems (Section 59.4.3). The photoreduction of Co^{III} complexes can be used to catalyze a number of solution development reactions. For example, $[Co(NH_3)_6]^{3+}$ can be photolyzed to Co^{II} and the image sequestered in a coating by a suitable chelating agent. The Co^{II} centers catalyze the reaction of H_2O_2 and a developer[164] (Section 59.3.3.1). Salicylaldimine complexes such as (**89**) when struck by light form catalytic centers, which accelerate the oxidation of color developers by molecular oxygen.[165] They can also form radical species used to initiate the polymerization of vinyl monomers such as acrylates or styrenes to give an imagewise distribution of polymer.[166]

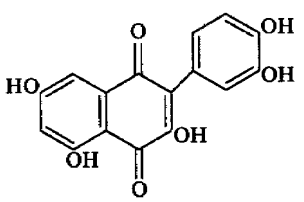


(89)

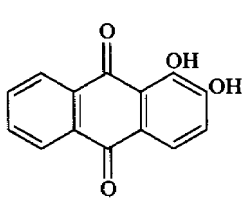
A number of imaging systems (so-called PD-D systems) based on the formation of an image in physically developable mercury nuclei have been reported by Philips Research Laboratories.[167] A common feature of these systems is that the photosensitive element contains an organic or inorganic compound that releases a ligand for Hg^{II} (CN^-, SO_3^{2-}, RS^-, NH_3) upon being struck by light. After exposure, the element is treated with a solution of an Hg^I salt. The disproportionation of Hg^I to Hg^{II} and Hg^0 is promoted in light-struck areas, and the Hg^0 nuclei can be subsequently physically developed.

Alternatively, photosensitive ferrioxalates such as $(NH_4)_3[Fe(C_2O_4)_3]$ together with mercury(II) chloride and ammonium oxalate have been used to produce physically developable nuclei. Treating an exposed coating with a physical developer containing ammoniacal silver nitrate produces a silver amalgam image and a dye image if a dye-forming developing agent is present.[168] Light exposure produces Hg_2Cl_2, which in the presence of ammonia disproportionates to Hg^{II} and Hg nuclei.[169] Ferrioxalates can also be used to produce Fe^{II} centers when exposed to light. Treatment with a silver nitrate solution produces Ag^0 nuclei, which can be amplified by a number of physical developers.

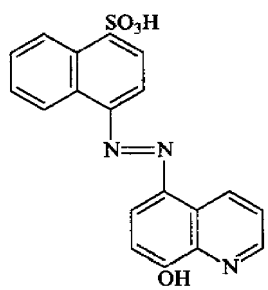
Photoconductors such as ZnO or TiO_2 can be used as the light-sensitive agent. After exposure, such elements are usually treated with a solution of a reducible metal salt (*e.g.* $AgNO_3$) to convert the transient photoconductor image into an image of physically developable metal nuclei. The spectral sensitivity of a substance like TiO_2 is limited to the ultraviolet. It can be extended into the visible by formation of complexes of TiO_2 with certain colored chelating agents. The chelating agents can form colored complexes with TiO_2 or they can be used to attach sensitizing dyes such as carbocyanine dyes to the TiO_2 surface.[170] Preferred chelating moieties are *o*-dihydroxyphenyl and 8-hydroxyquinoline groups. Examples of complex-forming spectral sensitizers include (**90**), (**91**) and (**92**). In a dye-bleach process, the dye–TiO_2 chelate serves as both spectral sensitizer and image dye.[171] Dye ligands (**93**) and (**94**) are used.



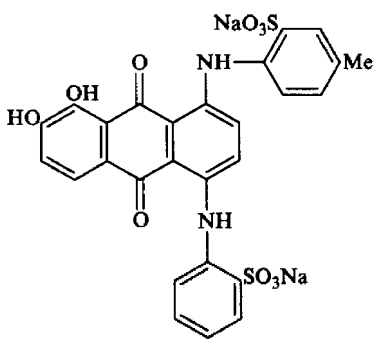
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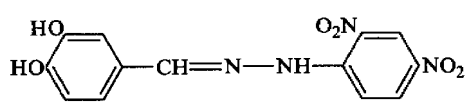
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(92)



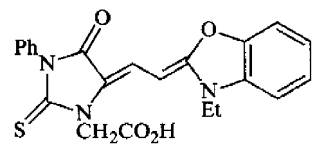
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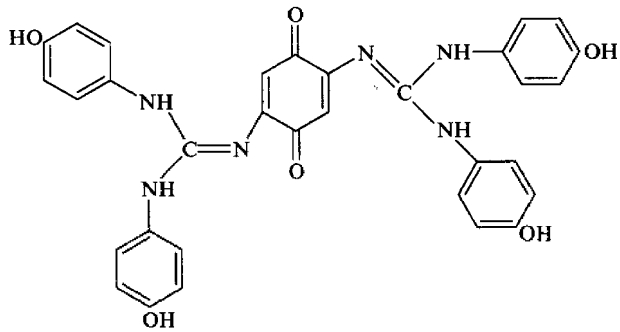
(94)

Non-specific complexes or associations between Ag^I and various cyanine spectral sensitizing dyes containing thiol or thione groups can be made by coating silver nitrate with a sensitizing dye.

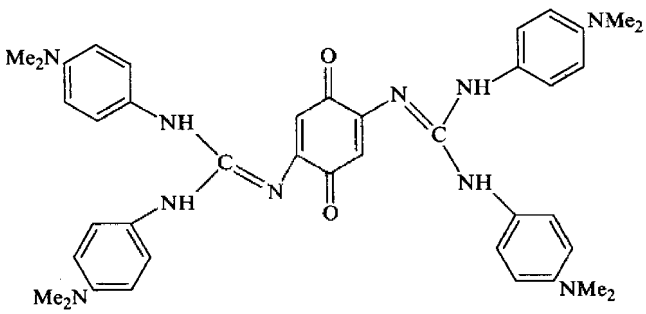
The coatings generate physically developable silver nuclei when exposed.[172] One example is the merocyanine dye (**95**).



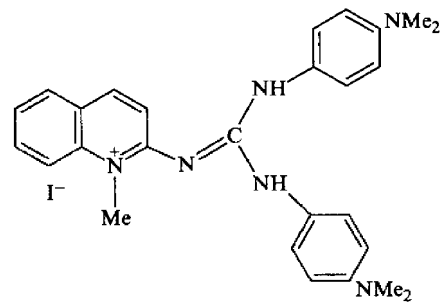
(**95**)



(**96**)



(**97**)



(**98**)

In another system, poorly defined complexes of Ag^I and guanidine derivatives such as (**96**) serve as the light-sensitive component. The complex serves as a light-sensitive element to form nuclei, a source of Ag^I for subsequent physical development and a source of aminophenol developer when it is activated by heat or in an alkaline solution.[173] In a variation of the process, merocyanine and cyanine dyes such as (**97**) and (**98**) are associated with Ag^I. Exposure again produces developable nuclei of Ag^0. Treating the material with heat or an alkaline processing solution fragments the ligands into developer and color coupler fragments. Where silver is developed, an image in dye is then generated.[174]

59.3.2 Physical Development Formulations

Physical development processes permit the use of less silver halide or the use of alternative, less expensive light-sensitive materials to form latent images. These images, in the form of suitable catalytic sites or nuclei, can be made visible by various physical development processes, although the speed or sensitivity of these systems falls far short of silver halide systems. One versatile method is to form an image by depositing a noble metal or other metal on the nuclei. The process can be practiced in several ways to produce images with various physical, optical, electrical or even magnetic properties.[4] A common characteristic of metal physical developers is that they consist of a thermodynamically unstable mixture of metal ions with a reducing agent. In the absence of catalytic nuclei, metal deposition is slow. In the presence of nuclei, metal is rapidly and spontaneously deposited.

Coordination chemistry plays a central role in the design and function of physical developer baths. Metal-complexing agents are present in most baths to control the activity of the metal ion and hence the electrochemical potential at which metal is deposited. Many baths operate under alkaline conditions, and complexing agents are then necessary to prevent metal hydroxide and oxide precipitation. Some baths contain a metal complex as the reducing agent or developer for the deposition of another metal; ligands are added to control the potential of the developer in these systems. Sequestering agents are sometimes present to complex with and thereby inactivate the unexposed latent-image-forming component of the imaging system. A few examples illustrate these applications.

In the RS process of Itek Corporation, a coating of a photoconductor such as TiO_2 is used to form upon exposure a reversible latent image, which is converted to a latent image in Ag^0 nuclei by treatment of the exposed TiO_2 with a silver nitrate solution. The coating can then be treated

with a solution of a Ag^I developer to produce a visible silver image.[175] The use of sequestering agents for Ag^I such as nitrilotriacetic acid [$N(CH_2CO_2H)_3$] or EDTA in the latent-image-forming process is reported to give improved densities with a number of physical developers (Ag, Cu or Sn).[176,177]

Silver physical developers have poor shelf stability and generally must be used shortly after preparation. With most silver-developer combinations, silver nuclei are formed after a short time (spontaneous nucleation), and these nuclei then rapidly catalyze the deposition of more silver, leading to rapid decomposition of the bath. Typical silver physical developers consist of silver nitrate, sodium sulfite, sodium thiosulfate and reducing agents such as isoascorbic acid, hydroquinones or aminophenols. Ammonia or other amines can be added to adjust the pH and perhaps adjust silver ion activity. Several complexes of Ag^I with sulfur-containing compounds can serve as sources of silver in physical development processes when in contact with a processing composition containing a developer. Suitable complexing agents include thioamides, thioureas, alkylthioacetic acids, various alkynes and thiols.[178] The complexes are generally coated together with the light-sensitive nuclei-forming material such as a silver–dye complex.

The stability of silver physical developers has been substantially improved by researchers at the Philips Research Laboratories. Their work has also led to the formulation of stable physical developers for the deposition of lead, tin, cobalt, nickel and indium. The applications of this technology in photoimaging and electronic photofabrication have been discussed.[167] Developer stability is improved by the use of appropriate cationic and non-ionic surfactants to adsorb to spontaneously formed nuclei in the bath and thereby prevent their growth. The rate of spontaneous nucleation in the bath is controlled by adjusting the activities of silver ion and the developer[179] (an Fe^{II}/Fe^{III} system consisting of iron(II) ammonium sulfate, iron(III) nitrate and citric acid). Some improved silver physical developers have a half-life of 120 days at room temperature. Others formulated with a half-life of 8 h will develop a latent image in 1–2 s at 55 °C. The photogenerated nuclei in the imaging elements are not initially accessible to the stabilizing surfactants, and thus initial development rates are rapid.

A useful copper physical developer consists of a mixture of a copper(II) salt [$Cu(NO_3)_2$], an amine such as triethanolamine to make the system basic as well as to sequester Cu^{II}, and a reducing agent (ascorbic acid). It can be used to develop Cu, Ag, Pd, Pt and Au nuclei.[180]

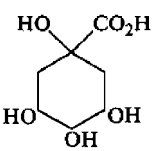
Copper physical developers containing the adjustable Fe^{II}/Fe^{III} redox couple are usable in the pH range 2–7. To render the Fe^{II}/Fe^{III} couple sufficiently potent reductively, complexing agents that selectively stabilize Fe^{III} but not Fe^{II} or Cu^{II} are used. Chelating phosphonic acids such as $Me_2CHN(CH_2PO_3H)_2$ work well. Other formulations contain complexing agents for Cu^I such as $HOCH_2C{\equiv}CCH_2OH$, HSO_3^- or MeCN. These permit use of Fe^{II}/Fe^{III} as the reductant for Cu^{II} salts in the presence of carboxylic acid sequestrants such as citric or malonic acids.[181]

Complexes of Cu^I halides with various oxazole or thiazole ligands can be used to produce copper images from physical developer baths in two ways. The first is conventional reduction by a reducing agent such as hydroquinone or ascorbic acid, generally in the presence of an amine base such as dimethylaminoethanol. Ag^0 or Pd^0 nuclei catalyze the process. In the second method, Ag^0 or Pd^0 catalyzes the disproportionation of the Cu^I complexes into Cu^{II} and Cu^0. A complexing agent for Cu^{II} such as triethylenetetramine is added to make the disproportionation thermodynamically favorable.[182]

Many physical developers are useful for amplifying Pd^0 nuclei. A wide variety of metals can be deposited, including nickel, cobalt, copper, iron and chromium. In general, the metal sulfate, nitrate or halide salt is mixed with a sequestering carboxylic acid such as malic, maleic, lactic, succinic, citric, tartaric, aspartic or hydroxyacetic acid. A reducing agent such as formaldehyde, NaH_2PO_2 or dimethylamineborane is added, and the pH is adjusted to 8.5–9.5 with NH_4OH. The solutions are stable, particularly when sequestering agents such as gluconic acid (**99**) or quinic acid (**100**) are present. The latter compounds sequester unexposed Pd^{II} from the film and prevent or retard its reduction by the developer to Pd^0 nuclei, which would lead to the rapid destruction of the processing bath.[183] Some of these developers are useful for developing Ag^0 and Cu^0 nuclei.[184,185]

$HO_2CCH(OH)CH(OH)CH(OH)CH(OH)CH_2OH$

(**99**)



(**100**)

59.3.3 Other Image Amplification Systems

In these processes, metal complexes find a number of uses as light-sensitive latent-image-catalyst formers, catalyst replacements for image silver in low-silver systems, and oxidants for various developers in image amplification baths.

59.3.3.1 Peroxide amplification systems

One system produces images by the catalytic decomposition of peroxy compounds (*e.g.* hydrogen peroxide) and the subsequent oxidation of a developer (a color developer or a cross-oxidizing developer). The catalysts can be an imagewise distribution of noble metal nuclei such as silver, platinum or palladium. The nuclei can be produced by the light-induced decomposition of a suitable complex or by brief development after exposure.[186] Several complexes of Fe^{III}, Co^{III} or Mn^{III} with oxalic, citric or tartaric acids form catalyst centers when struck by light, which catalyze the decomposition of peroxy compounds and hence promote oxidation of developer. For example, a coating containing ammonium tris(oxalato)ferrate(III) exposed to UV light and developed with an amplifying bath consisting of H_2O_2, a *p*-phenylenediamine developer and a pyrocatechol coupler forms a dye image in the areas struck by light.[187] Catalytic palladium nuclei are formed by the photodecomposition of sodium bis(oxalato)palladate(II) and amplified when developed with a mixture of 3-aminobenzidine, H_2O_2 and pyrocatechol.[158]

When a latent image or a faint image (partially developed) in silver is used in these peroxide/developer amplifying systems, it is important to keep the nuclei surfaces free of adsorbed inhibitors (for example, bromide ions), which may derive from other emulsion addenda. Inhibition or retardation of amplification can be circumvented by replacing the silver image with an image of another catalyst. One way of doing this is to bleach the silver image with a bleach–fix bath consisting of thiosulfate, sulfite and $[Co(NH_3)_6]^{3+}$. The Co^{III} bleaches the silver and remains in the emulsion layer in the vicinity of the original silver deposit by binding to gelatin. These cobalt(II) centers catalyze the redox reaction of hydrogen peroxide and a suitable color developer or cross-oxidizing developer.[188] The bleach–fix can occur before or concurrently with the peroxide amplification. The initial silver image development can be done separately or concurrently with the bleach step that establishes the image in Co^{II}. In fact, it is possible to carry out all three processes of silver image development, silver image bleaching by Co^{III} and peroxide amplification of the cobalt image with one processing solution.

The immobile catalytic cobalt(II) complex image can be used to establish an immobile catalytic manganese complex image useful in a reversal amplification process. The manganese complex catalyzes a peroxide/developer amplification reaction to form image dye. The process is applicable to low-silver materials and to non-silver imaging systems such as those in which photosensitized Co^{III} complexes form imagewise distributions of Co^{II} species when struck by light. For example, a coating may consist of a dye-forming coupler, a $[Co(NH_3)_6]^{3+}$ salt with a quinone photoreductant, a manganese(II) salt and 1-nitroso-2,4-dihydroxybenzene sodium salt to sequester the manganese. In exposed areas, Co^{III} is reduced to Co^{II} and preferentially complexes with the nitrosoresorcinol chelating agent, displacing Mn^{II}. In unexposed areas, Mn^{II} remains sequestered by the nitrosoresorcinol. The Mn^{II} complex is a much better catalyst for the H_2O_2 amplification reaction than is the Co^{II} complex formed in exposed areas. When the coating is then treated with a bath containing color developer and H_2O_2, dye forms in the unexposed areas faster than in the exposed areas, and a positive image results.[189] Other complexing agents are nitrosonaphthols or *o*-hydroxybenzaldehydes. The manganese(II) can be introduced after exposure and Co^{II} chelation.

Silver halide can be used as the light-sensitive component in the following way. A partially developed image in silver is bleach-fixed with a $[Co(NH_3)_6]^{3+}/S_2O_3^{2-}$ bath. The nitrosoresorcinol chelating agent in the film sequesters the Co^{II} image formed. The Mn^{II} present in the film or separately imbibed into the film generates a reversal image of Mn^{II} chelate where Co^{II} is not present. The H_2O_2/color developer amplification reaction is then carried out as described above.

59.3.3.2 Cobalt(III) amplification systems

In another interesting amplification system, an image in silver or other noble metal nuclei is used for catalysis, and a cobalt(III) complex is used as an oxidant in place of a peroxy compound. The amplification permits less silver to be used. An imagewise distribution of silver nuclei is associated with a non-diffusible dye-forming coupler, and the image is amplified by (1) imbibing the system with a solution containing a color developer such as a *p*-phenylenediamine and (2)

bathing the system with a solution of a Co^{III} complex[190] such as $[Co(NH_3)_6]^{3+}$. In the absence of silver nuclei the Co^{III} complex and the color developer react slowly. They react much more rapidly in the presence of silver metal centers. The Co^{II} formed in the catalyzed reaction is not itself a catalyst for the chromogenic reaction. The process has been expanded to include amplification of negative and reversal latent images in low-coverage silver halide multicolor photographic elements, using developer/amplifier baths containing both Co^{III} complex and color developer.[191]

Ligands that form colored complexes with the Co^{II} formed can also be introduced. These include 8-hydroxyquinoline, 1-nitroso-2-naphthol, and various formazan dyes. With a fixing agent such as thiosulfate added to the amplifier bath and adjustment of the levels of color developer and $[Co(NH_3)_6]^{3+}$, an effective monobath is prepared. Silver development and chromogenic dye formation and amplification occur early in the process, and as time progresses the thiosulfate fixes out the undeveloped silver halide and promotes the eventual oxidation (bleaching) of silver image by Co^{III}. Thus a single processing solution provides a dye image and effectively bleaches and fixes the silver.[192]

Several other imaging systems based on Co^{III}/developer amplification are known, including systems with various diffusion transfer imaging chemistries. The principles are the same as those outlined here. Basically, most imaging chemistries useful with silver halide systems can be transformed into a low-silver or (sometimes) non-silver system with a suitable developer/Co^{III} complex redox combination for amplification on imagewise catalytic nuclei.

At pH 11–13, several Co^{III} complexes including $[Co(NH_3)_6]^{3+}$ will react with and harden or crosslink an unhardened gelatin layer, a process catalyzed by silver metal nuclei. Although this is not a dye-forming amplification process, the differentially hardened gelatin layer absorbs and then transfers liquid dyes to laminated receivers in an imagewise fashion.[193] This 'tanning' or crosslinking process can be improved by using tanning developers such as various *o*-dihydroxybenzenes with the Co^{III} complexes in a developer bath.[194]

59.4 PHOTOTHERMOGRAPHY

In photothermography, a latent image formed by light exposure is converted into a viewable image by heat. No external solutions are used, and all components are preferably contained in the imaging material. Many references are made in the patent literature to photothermographic systems in which metal complexes are either preformed or generated during the imaging process.

A desirable property of a photothermographic system is the ability to amplify the light exposure during the thermal process, thereby increasing the photographic speed.[195] Thus the product of the photochemical step should catalyze the thermal reaction.

59.4.1 Silver-based Systems

The most commonly used process is based on silver. In dry-silver films and papers, silver behenate or a similar long-chain acid salt is coated in the presence of a small amount of halide ion or silver halide.[196] When the film or paper is exposed to light, a latent image is generated in the silver halide, which provides an autocatalytic site for the deposition of silver from the silver behenate. When the element is heated (a reducing agent such as hydroquinone is present), a negative image is generated. Instead of silver behenate as the silver ion source, silver complexes can be incorporated, provided that the gross stability constants for the complexes fall between certain limits.[197] These silver complexes must act as a source of silver metal for the image and must therefore be reducible. However, if the stability constant β is below 4.5, the system has poor shelf life and is unstable to heat in areas unexposed to light. Conversely, if $\beta > 10$, the complex is too strong and cannot be reduced under the reducing conditions prevailing in the coating. A variety of suitable complexes are described, with the preferred ones being formed from imidazole and 1-ethylimidazole.

Incorporation of nickel or cobalt complexes into a silver-behenate-based imaging system is reported to stabilize it to the effects of heat and humidity.[198] Among the complexes disclosed are $Co(acac)_2$ and bis(salicylaldoximato)nickel(II).

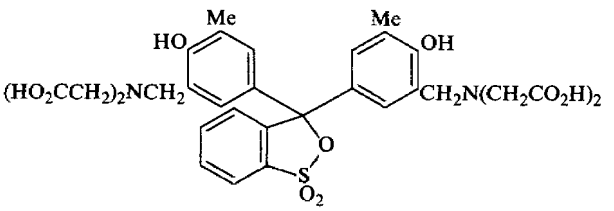
Palladium compounds have also been reported to stabilize unexposed areas to heat.[199] The compounds disclosed include the complexes of triphenylphosphine, bipyridine, acetylacetone and dimethylglyoxime. Preferred compounds appear to be the acac analogs.

In a photothermographic system disclosed by Itek Corporation, the light-sensitive element is a silver halide and the image-forming material is the silver salt of EDTA or a related compound.[200]

On heating, the silver nuclei formed during light exposure catalyze the decomposition of the silver salt, thereby amplifying the image.

59.4.2 Iron-based Systems

The imagewise photochemical generation of iron(II) from various processes can be used as a basis for imaging systems.[201] Ferrioxalate salts are photosensitive and generate Fe^{II} oxalate on exposure to light from a high-pressure mercury lamp. By incorporating metallizable dyes into an imaging element containing the ferrioxalate salt, image discrimination can be obtained after exposure by developing with water.[202] Differences in absorption spectra of the Fe^{III} and Fe^{II} complexes of the dye xylenol orange (**101**) under acid conditions give a positive-working system with a violet image on a yellow background.



(**101**)

In another system the photosensitive element consists of ferrocene or a substituted ferrocene coated in a layer with a bidentate ligand such as phenanthroline. After exposure, the coating is heated and the iron(II) reacts with the ligand to form the dye complex in the exposed areas; in the unexposed areas the ferrocene is volatilized out of the coating, thereby fixing the image.[203] If a polycarbonate matrix is used, the exposed areas become conductive, and multiple copies can be made from a single exposure by electrographic imaging.[204]

59.4.3 Cobalt-based Systems

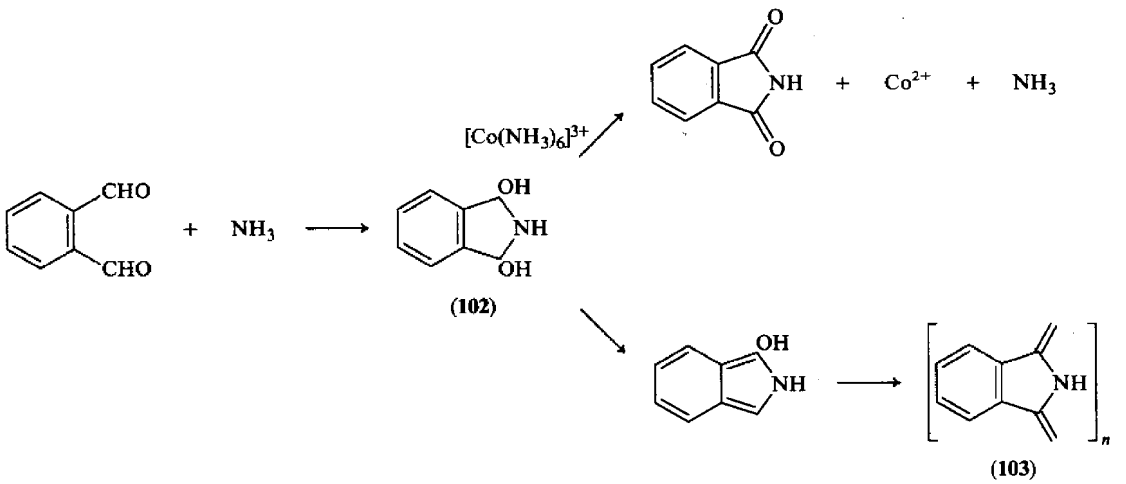
Much work has been done with Co^{III} complexes, using the Co^{III}–Co^{II} redox couple to obtain amplification, and more than 100 patents discuss ways of imaging using cobalt(III) complexes. As an example, consider an imaging element containing a cobalt(III) hexaammine complex, a conjugated π-system that forms at least a bidentate colored chelate with cobalt(III), a photoreductant such as a quinone, and a hydrogen donor. In areas of light exposure the quinone is reduced to give a species that when heated reduces the cobalt(III) hexaammine complex to cobalt(II). This kinetically labile cobalt(II) species now forms a complex with the conjugated π-system and then reduces neighboring cobalt(III) hexaammine complex, producing a stable cobalt(III) dye complex. This is a self-catalyzing process and continues until one of the reactants is used up.[205] Many different cobalt(III) complexes may be used; however, the most popular one is cobalt(III) hexaammine trifluoroacetate. Examples of a conjugated π-system are 1-(2-pyridylazo)-2-naphthol and phenanthroline. This is a negative-working system because dye is generated in exposed areas.

In other imaging systems, ammonia or other amines are thermally released from the cobalt(III) complex upon reduction. This imagewise release can be monitored either as a pH change, causing a color-forming reaction, or by incorporating into the system a component such as *o*-phthalaldehyde, which reacts with ammonia to form a black dye.

The proposed mechanism for dye formation is shown in Scheme 2. The initial step is the reaction of phthalaldehyde and ammonia to form the intermediate (**102**), which can either dehydrate and polymerize to form the oligomeric dye mixture (**103**; $n = 2$–6) or reduce cobalt(III) hexaammine, thereby releasing more ammonia and amplifying the response.[206–208]

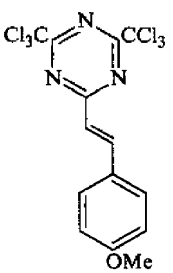
The ammonia or other amine can also be used to activate a diazo color-forming process in a separate or adjacent layer.[209] The image can be amplified by using the released amine to activate reductant precursors such as quinones and hydroquinones. Both positive and negative images can be produced by using appropriate imagewise and uniform exposures.

Instead of promoting ammonia release by light exposure, it is possible to inhibit it by incorporating a photoinhibitor such as a photolytic acid generator and a reductant in place of the photoreductant. Useful photoinhibitors are heterocyclic compounds containing at least one trihalogenated alkyl group such as (**104**). It is not known whether the acid generator functions by



Scheme 2

preventing the release of ammonia from the cobalt(III) hexaammine complex or by neutralizing it when formed. Many different examples are described, but one will suffice to illustrate the system.[210]



(104)

Cobalt(III) hexaammine trifluoroacetate is coated together with iodoform (photolytic acid generator) and 4-phenylcatechol (reductant). An imagewise exposure is made, and the exposed film is then placed face-to-face with a base-activatable diazo recording layer. Upon heating, ammonia is liberated in the unexposed areas and a positive image is formed in the diazo layer.

A multicomponent positive-imaging process using ammonia release has been described by Ricoh.[211] The components of the system are: (1) a cobalt(III) hexaammine complex, (2) a quinone photoreductant, (3) a chelating agent such as dimethylglyoxime, (4) a leuco dye (triarylmethane type), (5) a photooxidant (biimidazole) and (6) an organic acid (toluenesulfonic acid).

The stated mode of operation is as follows. Exposure to light initiates the same reactions as described previously. However, the chelating agent is chosen such that its cobalt(III) complex has a low extinction coefficient in the visible. The reduction of the initial cobalt(III) complex liberates ammonia, which neutralizes the acid in the exposed areas. After these changes have been brought about in the heating step, a UV exposure activates the photooxidant, which in turn oxidizes the leuco dye only where acid is still present. These areas correspond to those that did not receive an exposure originally, thereby producing a positive image of the original. Alternatively, negative images can be produced by an imagewise UV exposure followed by a uniform visible exposure. Heating then fixes the image.

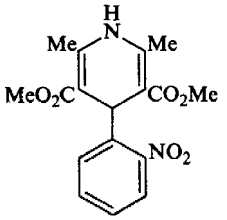
Despite all the work and patent activity with cobalt complexes for photothermographic and related processes, no commercial product is on the market.

59.4.4 Tellurium-based Systems

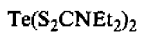
Various tellurium compounds have been used in photothermographic systems. For references to earlier work, see the publications by Gysling and coworkers.[212–214]

In one type of photochromic tellurium imaging element, a Te^{IV} compound is coated with a photoreductant.[215–218] As a result of light exposure followed by heating, the tellurium compound is converted to metallic tellurium. A typical composition comprises bis(acetophenone)tellurium dichloride and benzoquinone. Presumably the process goes through the Te^{II} derivative, which decomposes spontaneously to Te^0 on heating. This is a negative-working process, but it can be

modified to provide a positive image if a photooxidant is incorporated into the system together with a reductant. The photooxidant inactivates the reductant in areas of light exposure, so that Te^0 is generated only in the unexposed areas.[219] A typical photooxidant is the dihydropyridine (**105**).



(**105**)



(**106**)

Compounds of Te^{II}, such as the dithiocarbamate (**106**), can be used in combination with a reducing agent in a photothermographic system that incorporates benzenetricarbonylchromium as the photosensitive component.[220] Other ways of initiating the thermographic decomposition of the dithiocarbamates include the photogeneration of catalysts such as Ag^0 and Pd^0; these are described in several patents.[221]

59.4.5 Diazo and Other Systems

A diazo process in which one of the reactants is a metal β-diketonate has been reported. A light-sensitive diazonium salt is coated in a layer with a metal β-diketonate.[222] The advantage described for this system is that after the light-induced destruction of the diazo compound in the image area, the unexposed area can be developed by heat alone without the need for alkali treatment or for the presence of base-generating material. Some of the examples given are $[Ti(acac)_3]_2[TiCl_6]$, $Sn(acac)_2Cl_2$ and $MnO_2(acac)_2$.

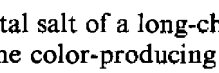
A photothermographic image transfer system has been described in which 4-methoxy-1-naphthol is immobilized in a layer as a function of light exposure.[223] Thermal transfer of the naphthol from the unexposed areas to a layer containing a leuco phthalocyanine reduces it to a phthalocyanine dye, thereby producing a positive image of the original.

59.5 THERMOGRAPHY

59.5.1 Physical Separation of Reactants

In thermographic processes, no light exposure is required and image discrimination is made thermally, and the patent literature contains many examples of systems in which colored metal chelates are formed by heat. In most cases the structures of the complexes are not defined. The important feature of all the systems is the manner by which the reactive components are kept apart until heat is applied.[224]

In one system, the reaction of the metal salt of a long-chain fatty acid with diphenyl-carbazide or -thiocarbazide (**107**; X = O, S) is the color-producing step.[225] The two components are ball milled separately in the presence of a film-forming binder, then mixed and coated on a suitable support. Many different components are possible, as long as the main criterion that one of the pair should melt between 60 and 120 °C is satisfied. After a thermal exposure to the original, the image produced from copper stearate and diphenylcarbazide is purple with a tan background. The coated materials should not absorb infrared radiation, or image discrimination will be lost. A later patent reports essentially the same material but with different binders and additives to improve storage.[226]



(**107**)

Another way to keep the reactive components separate is encapsulation, in which either or both of the components are covered with a layer of low-melting material such as stearic acid or paraffin wax.[227] Several tridentate azo dyes are reported as color-forming chelating agents as well as some esters of gallic acid.

59.5.2 Decomposition of Image Former

Thermographic elements utilizing both Te^{II} and Te^{IV} compounds have been described.[228,229] Imagewise heating of a Te^{IV} compound such as (**108**), usually in the presence of a reducing agent, produces elemental tellurium.

$$TeCl_2(CH_2COPh)_2$$

(**108**)

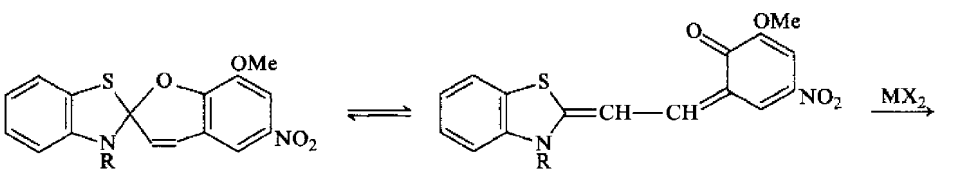
A thermographic material with only one heat-sensitive component is prepared by reaction of an organometallic compound such as phenylmercury(II) nitrate with a thiourea derivative.[230] The product is ball milled and coated in a binder such as poly(vinyl acetate). Other organometallic compounds disclosed are those of bismuth, tin, gallium and germanium combined with a variety of sulfur-containing compounds such as thioamides and xanthates.

59.5.3 Transfer of Reactant

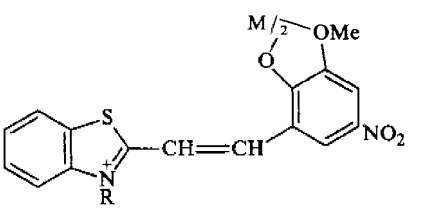
An alternative way to produce an image thermographically is by transfer of a volatile reagent to a receiver sheet containing another reagent, usually a metal ion.[231] Thus a system comprising *N,N'*-dibenzyldithiooxamide as the volatile component and a nickel salt gives a dark purple image after transfer.

59.5.4 Thermochromic Spiropyran

The thermal equilibrium (Scheme 3) between the open and closed forms of a spiropyran is the basis of a thermographic system by NCR Corp.[232] The spiropyran (**109**) is coated with a metal salt of a fatty acid and a binder. On heating, the spiropyran is converted into the open merocyanine form, while the melting of the salt allows formation of a complex (**110**), preventing return to the spiro form.



(**109**)



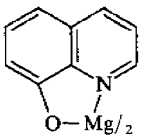
(**110**)

Scheme 3

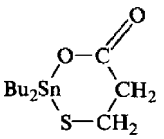
59.6 ELECTROPHOTOGRAPHY

59.6.1 Photoconductors

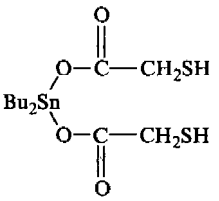
Metal chelates of 8-hydroxyquinoline such as (**111**) with photoconductive properties are reported to be useful in electrophotographic systems.[233] The incorporation of a tin complex into a photoconductive zinc oxide layer is stated to reduce 'dark decay'. In other words, the electrostatic charge applied to the photoconductor has a longer lifetime. Two of the complexes disclosed for this application are (**112**) and (**113**). These compounds are prepared from dibutyltin oxide by reaction with 2-mercaptopropionic acid and thioglycolic acid, respectively.[234]



(111)



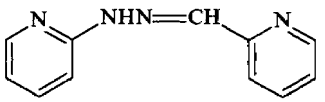
(112)



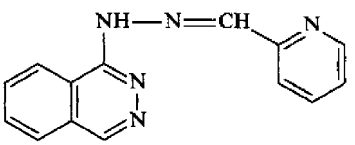
(113)

59.6.2 Optical Sensitization

An inorganic photoconductor such as zinc oxide can be optically sensitized by treating it with a ligand that will form a colored zinc complex. The resulting material then responds to light of the wavelength where the complex absorbs. Suitable ligands are prepared by the condensation of heterocyclic hydrazines and heterocyclic aldehydes.[235] Two examples of the more than 50 disclosed in the patent literature are (**114**) and (**115**).



(114)



(115)

59.6.3 Protective Coatings

In indirect electrophotography, where the image of toner formed on the surface of the photoconductor is transferred to a suitable support, usually paper, it is necessary to clean the residual toner from the surface of the photoconductor. If this is done by brushing, the surface may be damaged, and among the various solutions to this problem is a polymeric layer containing an aluminum chelate coated on the photoconductor.[236] This has a twofold effect: the photoconductor is protected from abrasion and the transfer rate of toner from donor to receiver is enhanced. Two of the aluminum complexes with ethyl acetoacetate used for this application are $Al(MeCOCHCO_2Et)_3$ and $Al(OCHMe_2)_2(MeCOCHCO_2Et)$.

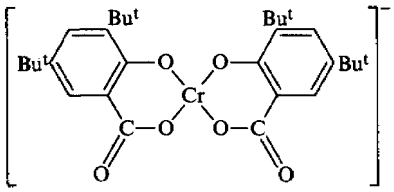
59.6.4 Planographic Printing Plate

In the preparation of a printing plate electrographically, the photoconductor consisting of zinc oxide in an electrically insulating binder has an electrostatic image generated on it. The development toner consists of fusible hydrophobic particles. After fusion, the hydrophobic/hydrophilic nature of the image allows differentiation to be made by printing with a hydrophobic ink. To improve the hydrophilicity of the undeveloped areas, the recording layer can be treated with a ligand that will form a hydrophilic chelate with zinc ions from the zinc oxide photoconductor or with a preformed zinc chelate.[237] Suitable ligands are (**114**) and (**115**). The copper(II) and cobalt(II) chelates of these ligands can also be used.

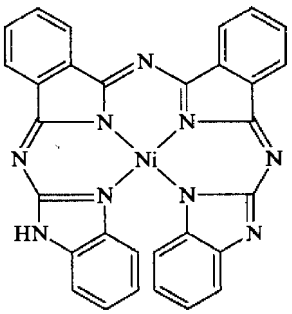
59.6.5 Toners and Charge-control Agents

For an electrographic toner to function optimally, the particles must all have the same charge. The incorporation of a chromium complex of a salicylic acid derivative into a toner formulation using a variety of binders provides a negatively charged toner. One favored example is the 1:2 complex of Cr^{III} with 3,5-di-*t*-butylsalicylic acid (**116**). A pigment such as copper phthalocyanine can also be incorporated in this formulation to give a colored toner.[238] Conversely, a positively charged toner can be obtained by incorporating into the toner a complex of a metal ion with EDTA. Complexes of bivalent, trivalent and tetravalent ions are described as being effective.[239]

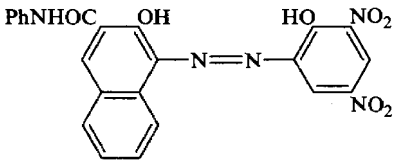
In a variant of electrographic image reproduction that uses electrically photosensitive particles for image formation, certain nickel complexes such as (**117**) are reported to be advantageous



(116)



(117)



(118)

because particles containing them have such broad light sensitivity that they do not have to be spectrally sensitized.[240] Chromium(III) complexes of azo dyes used as black toners are described as giving bright fog-free images.[241] The 1:2 complexes of an azo naphthol dye such as (**118**) are disclosed.

59.7 MISCELLANEOUS USES

59.7.1 Non-catalytic Imaging Systems

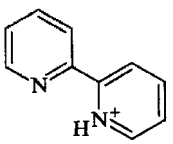
High-sensitivity photographic systems are based on the formation of an imaging catalyst or a catalyst precursor as a result of exposure to electromagnetic radiation. The latent-image catalyst is subsequently amplified by chemical development. The development reaction generally produces a metal-deposit image, a dye image or sometimes an image in polymer or crosslinked polymer. Some photographic systems produce images directly as a result of exposure to light, with no amplifying development. In silver halide systems they are not very important. However, with other light-sensitive materials, including some of those used in physical development processes (Section 59.3.2), particularly the inexpensive ones, some useful non-catalytic processes have been developed.[2–5]

Among the systems using coordination compounds, perhaps the most significant is the well-known blueprint process based on the photolysis of Fe^{III} compounds. In this process a paper is impregnated with a solution of $K_3[Fe(CN)_6]$ and an Fe^{III} complex of a polybasic acid such as citric or oxalic acid. Exposure to actinic light reduces the Fe^{III} carboxylate complexes to Fe^{II} complexes. Washing the paper with water produces blue $KFe[Fe(CN)_6]$ in exposed areas. The $K_3[Fe(CN)_6]$ is less sensitive to light than the Fe^{III} carboxylate complexes. The small amounts reduced to $[Fe(CN)_6]^{4-}$ by exposure produce some insoluble white $K_2Fe[Fe(CN)_6]$ in exposed areas after washing. In unexposed areas, the washing removes unreacted salts and complexes. After this, a solution of dichromate is used to oxidize the white $K_2Fe[Fe(CN)_6]$ to more blue $KFe[Fe(CN)_6]$. Owing to the toxicity of $[Fe(CN)_6]^{3-}$, this process is not popular today.

Other iron-based photographic systems have been devised. For example, the complex (**119**) can be coated with a suitable binder. Exposure reduces Fe^{III} to Fe^{II}. Treating the coating with water produces intensely colored Fe^{II} bipy complexes in exposed areas and washes unreacted salt out of unexposed areas.[242] A system in which a ferrioxalate complex is photolyzed to form Fe^{II}, which is then selectively complexed with a dye indicator, was discussed in Section 59.4.2.[202] An obsolete 'palladiotype' process relied on the photolysis of ferrioxalate complexes to produce Fe^{II}, which in turn reduced a Pd^{II} salt to produce an image in Pd^0. More economical and sensitive processes today are based on amplifying a weak image in Fe^{II} or palladium nuclei by physical development.

59.7.2 Relief-image-forming Systems

The ability of Fe^{III} salts to crosslink colloids such as gelatin can be used to produce a relief image in the colloid, useful for graphic processes such as lithography. A coating can be made of gelatin,



$[Fe(C_2O_4)_2(H_2O)_2]^-$

(119)

a simple crosslinking iron(III) salt such as $Fe(NO_3)_3$, a more light-sensitive non-crosslinking complex iron(III) salt of a dicarboxylic acid such as ammonium tris(oxalato)ferrate(III), and a volatile acid to make the mixture coatable. When the coating is dried, the free iron(III) ions crosslink and uniformly insolubilize the gelatin under neutral conditions. After the coating is exposed to actinic radiation, a positive or negative relief image can be obtained, depending upon processing. Washing the film with water produces a positive image. Presumably the crosslinking Fe^{III} ions are reduced to less strongly complexing Fe^{II} in exposed areas, and the gelatin is solubilized. The reduction may occur by way of the more light-sensitive ferrioxalate complexes. A negative image results if the exposed coating is treated with acidic hydrogen peroxide, which decomposes in the exposed areas containing Fe^{II}. Decomposition products crosslink the gelatin, thereby hardening it in exposed areas. The acidic solution removes Fe^{III} and unhardened gelatin from the coating.[243]

Light-sensitive carboxylate complexes of Fe^{III} have been used to generate vinyl polymerization initiators in relief-imaging systems. The Fe^{II} generated in light-struck areas produces polymerization-initiating hydroxyl radicals when treated with peroxy compounds.[244]

Photopolymerizable coatings have been prepared containing vinyl monomers and a mixture of $NaMnP_2O_7$ and Fe^{III} oxalate, which photogenerates polymerization-initiating $\cdot CO_2^-$ radicals.[245]

Colloid layers such as gelatin, albumen, starch, glues and poly(vinyl alcohol) can be imagewise hardened or tanned by exposing coatings containing dichromate salts. This is still an important method of producing negative relief images. The chemistry and applications of these systems have been reviewed.[2] The relief-image systems are used in a number of printing, lithographic and photoresist applications.

The ammonia or amine photothermally liberated from a cobalt(III) complex can be used to crosslink a carbonyl-containing polymer. One such complex is (**120**), which can be used in a photoresist composition where the non-crosslinked polymer is dissolved away, leaving a negative image in hardened polymer.[246]

$$Co\{NH_2(CH_2)_3NH_2\}_3(CF_3CO_2)_3$$

(120)

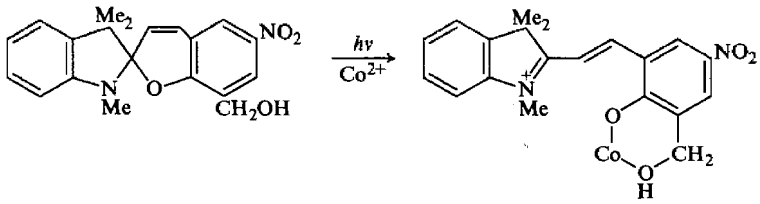
Photoresist systems in which a photosensitive polymer is imaged over a metal coating on a support are of great importance for electronic applications. The use of aluminum in such an application requires a developing solution that will etch it despite the tendency for aluminum to form an oxide coating. Use of chelating agents with stability constants for Al^{III} above 6.7 in pH 13 developing solutions speeds the etching of the aluminum.[247] Sulfosalicylic acid and EDTA are both reported to be effective.

59.7.3 Photochromic Systems

Many organic and inorganic compounds change color when exposed to actinic radiation and return to their original color in a dark reaction. These reversible color changes are characteristic of photochromic compounds. In a photographic system the reversibility of photochromism may or may not be desirable. To produce a permanent image from such material, the reverse reaction must be stopped, or alternatively, the transient image must be converted into a more permanent image before it disappears. Reversibility is desirable in systems requiring reuse of the radiation-sensitive element. One way in which a photochromic reaction can be stabilized or made less reversible is by metal complex formation with the reaction product, as shown in equation (2). For example, the photochromic spiropyran (**121**) isomerizes to a merocyanine dye when struck by light. The dye can form a complex (**122**) with various metal ions such as Zn^{II}, Cu^{II} or Co^{II} and is thus less able to return to its spiropyran form.[232,248,249]

59.7.4 Vesicular Imaging Systems

Complexes of oxalic, citric or tartaric acids with Fe^{III} can be used as the light-sensitive and gas-bubble-producing components in vesicular imaging systems. In the vesicular process, an image



(2)

(121) (122)

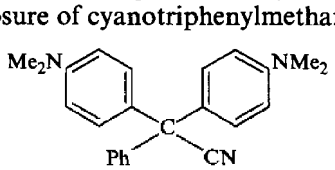
is formed in a suitable coated binder by light-scattering bubbles produced by a gas-generating compound coated therein.[2] In many systems, diazonium compounds are used to photolytically generate N_2, but systems based on the imagewise generation of CO_2 by the photolytic decomposition of ferricarboxylate complexes have also been devised.[250,251] Areas of the film struck by light produce an image in Fe^{II} and minute light-scattering CO_2 bubbles. Alkylcarboxylatodichlorochromium(III) complexes of long-chain fatty acids have been used in vesicular imaging elements to stabilize the coatings to high temperature and humidity after processing. Presumably the heat applied during the development of expanded bubbles in the coating crosslinks the binder with Cr^{III}, producing a thermoset structure of improved stability.[252]

A different vesicular photoimaging material consists of an assembly of lipid vesicles sensitized with rhodopsin. In one system the vesicles can be filled with a solution containing Co^{2+}, and the solution outside the vesicles can be free of metal ions but contain a chelating indicator dye such as xylenol orange (**101**). The whole assembly can be coated, and when exposed to actinic radiation the vesicles are disrupted in exposed areas and release Co^{2+} ions, which are complexed by the dye indicator, thereby forming an image.[253]

59.7.5 Enzymatic Imaging Systems

Since enzymes are catalysts, they can be used as amplifiers to form an image, provided there is some way to activate or inactivate them as a function of light exposure. Protease enzymes, which hydrolyze protein, can be used to produce relief images in gelatin coatings containing the enzyme. Metal complexation has been used to crosslink, denature and thereby inactivate the enzyme papain by mixing it with $HgCl_2$. Gelatin coatings containing this modified enzyme are reported to be stable. Areas of the coating exposed to light are hydrolyzed and washed away in a subsequent water wash, because the enzyme has been regenerated or activated by light exposure.[254]

In another system, catalase or peroxidase enzymes can be used to produce an image in minute O_2 bubbles (vesicular image) or an image in dye produced by the catalyzed reaction of a peroxy compound and a leuco dye, or a color developer in the presence of a dye-forming coupler. The enzymes are inactivated in areas exposed to light. In one system the metalloenzymes are poisoned by CN^- photodissociated by exposure of cyanotriphenylmethane compounds[255] such as (**123**).



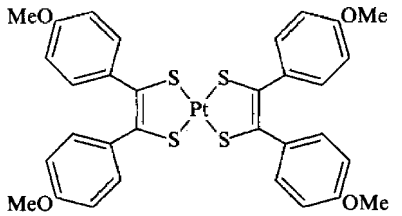
(123)

59.7.6 Optical Recording Systems

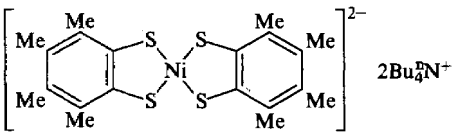
In one recording medium, a light-reflecting layer is overcoated with a light-absorbing layer formed by vacuum deposition of a phthalocyanine dye. Lead, chloroaluminum, vanadyl and tin(IV) complexes are used. Upon irradiation by an AlGaAs solid-state injection laser operating in the 750–850 nm range, the absorbing layer is ablated or vaporized, leaving a hole that exposes the light-reflecting layer. Readout is done with a less intense laser that will not vaporize the absorbing layer.[256]

Another patent describes an advantage for a light-absorbing layer that contains a platinum complex of an alkene-1,2-dithiolate (1,2-dithiolene) such as (**124**) because of an inherently greater volatility.[257]

The benzenedithiol nickel complex (**125**) absorbs radiation in the 800–950 nm range. This material, when dispersed in an organic vehicle and coated on a polyester support, is reported to be suitable for recording with a GaAs laser.[258]



(124)



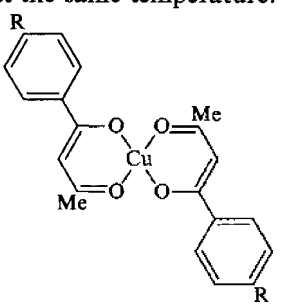
(125)

59.7.7 Electron Recording Systems

The combination of a cobalt(III) hexaammine complex and a chelating compound such as 1-(2-pyridylazo)-2-naphthol functions as a recording medium for electron exposures in a vacuum.[259] A low-level exposure produces a latent image that can be amplified by heating, whereas higher exposures give a visible printout image. A coating containing $Fe(acac)_3$ and 4,7-diphenyl-1,10-phenanthroline also functions as an electron-beam recording medium.[260] Upon irradiation, a magenta iron(II) chelate is formed, which is intensified by heating.

59.7.8 Erasable Thermal Recording System

In one erasable recording medium, a transition metal complex such as (**126**) is mixed with a polymer so that a domainal film is formed.[261] Fusion and quenching of the film give a transparent glassy state. Selective heating with a thermal pen generates the crystalline state. The record is erased by another fusing and quenching sequence. A required property of the complex is that the glass-transition temperature and the crystallization temperature must be similar. Also, the complex must be able to be glassy and crystalline at the same temperature.



(**126**) R = C_7–C_{12} alkyl

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60

Compounds Exhibiting Unusual Electrical Properties

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60.1 INTRODUCTION

The vast majority of metal complexes in the solid state are insulators and do not exhibit any interesting electrical conduction properties because the metal atoms are surrounded by 'insulating' ligands which prevent the passage of carriers from one site to another. This review will be limited to a discussion of the electrical conduction properties of coordination compounds, and will not include simple inorganic compounds with high electrical conductivity such as mixed metal oxides, β-alumina and $TaSe_3$.

Widespread interest in the electrical conduction properties of metal complexes is a fairly recent phenomenon. In the 1960s a number of papers appeared which dealt with the conduction properties of complexes and pointed the way for future studies.[1–3] It was realized that for conduction to occur in a complex it is necessary for there to be some form of electronic, as opposed to magnetic, interaction between either the metal atoms alone or the complexes as a whole in the lattice. The presence of an interaction of this type is revealed by the presence of strong absorption bands at lower energies than those present in the isolated metal complexes in solution.[4,5] However, the presence of new intense absorption bands in the solid state does not necessarily promise high electrical conductivity, but in the absence of these additional absorptions the complex is most likely to be an insulator. For high conductivity to be present the interaction between the metal atoms of complexes must extend throughout the solid and not be restricted to the dimer or cluster formation, since the spaces in the lattice between the delocalized clusters will be insulating. In coordination compounds as opposed to simple compounds it is very difficult to envisage interactions leading to conduction pathways in three dimensions and, therefore, the complexes with unusual electrical properties are anisotropic. By far the most common types are systems known

as 'one-dimensional conductors'. This is a reflection of the common building block, a square coplanar complex, found for this class of compound.

For significant electrical conductivity in a metal complex there has to be the correct combination of both structural and electronic features.

(i) Structural

As described previously, the shape of the complex must be such that extensive inter-complex interactions can occur in the solid state. For this reason, columnar stacked structures involving square coplanar complexes and allowing effective intrastack interactions are most commonly found in compounds of this type. Electron transport will be facilitated by the close approach of the complexes and therefore the absence of bulky non electroactive ligands is an advantage. Detailed structural studies have shown the importance of interstack interactions (*e.g.* H-bonding, ligand–ligand bonding) in stabilizing these structures, and these interactions can also have an important bearing on the electrical conduction properties.

(ii) Electronic

Complexes can conveniently be divided into those that show only semiconductor-type behaviour and those that show metallic behaviour, possibly restricted to a certain temperature range.

(a) Semiconductors. Semiconductors are characterized by relatively low conductivities and a positive temperature dependence of the conductivity, and most complexes which exhibit detectable electrical conductivity belong to this class. In general, this type of behaviour is found for complexes containing metal ions in integral oxidation states.

In columnar stacked one-dimensional complexes, such as the tetracyanoplatinates, with relatively short intrachain Pt—Pt separations, it is possible to postulate a simple band model by considering overlap of the filled $5d_{z^2}$ orbitals on individual atoms in the chain to produce a full $5d_{z^2}$ band, and overlap of the empty $6p_z$ orbitals to produce an empty $6p_z$ band (Figure 1).

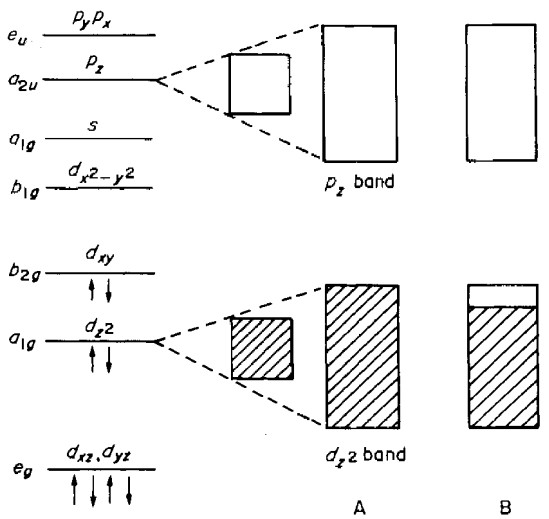


Figure 1 Schematic representation of the band formation in a columnar stack structure. (A) Semiconductor based on integral oxidation state d^8 complex. (B) One-dimensional metal produced by partial oxidation and resulting in a 'non-integral' oxidation state

The intrinsic band gap is too great to account for the observed conductivities and the presence of Pt^{IV} impurities, which create acceptor levels within the band gap, has been found in related systems.[6] The temperature dependence of the conductivity as given by

$$\sigma = \sigma_0 \exp[-(\Delta E/kT)]$$

(where σ is the conductivity, σ_0 a constant and ΔE the activation energy) is often obeyed for these systems.

An alternative model considers the carriers to be localized on individual molecules, and that charge transfer occurs by the carrier 'hopping' between these localized centres. The hopping process involves the charge carrier overcoming a potential energy barrier and thus involves an activation energy for conduction.[7] The temperature dependence of this conductivity may depend on the dimensionality of the system.[8]

(b) Metals. Complexes which exhibit metallic properties have been extensively investigated over the last 15 years and many examples will be discussed in this chapter. For metallic properties there must be an odd number of electrons per site. In general, for a one-dimensional metallic complex a non-integral number of electrons per site is required. This is best illustrated by reference to the Krogmann salt $K_2[Pt(CN)_4]Br_{0.3}\cdot 3.2H_2O$. In this compound the $[Pt(CN)_4]^{1.7-}$ ions form a columnar stacked structure with a very short intrachain Pt—Pt separation (2.88 Å). Overlap of the $5d_z$ and $6p_z$ orbitals on adjacent platinum atoms in the chain leads to the formation of a delocalized band structure. Because of the non-integral charge on the ion the band is only approximately 7/8 filled, resulting in one-dimensional metallic properties (optical, magnetic and transport) at room temperature (see Section 60.2.1).

Peierls predicted that a 1D system would be inherently unstable with respect to a lattice distortion in the metal atom chain direction (Figure 2).[9] This Peierls distortion (PD) would split the partially filled band into filled and empty bands of lower and higher energy respectively, thus lowering the total electronic energy of the system. The period of the PD will depend on the degree of band filling and therefore, in the case of a one-dimensional metallic complex, on the degree of partial oxidation (DPO) of the complex. Thus the Peierls distortion converts a 1D metal into a semiconductor by opening up a band gap at the Fermi surface. The band gap will be twice the activation energy for conduction in the semiconductor region. Peierls' argument is for the zero-temperature case, and at some finite temperature well above absolute zero the band gap becomes temperature-dependent, and at some higher scale temperature (T_P) the band gap will disappear and the system will display metallic transport properties.

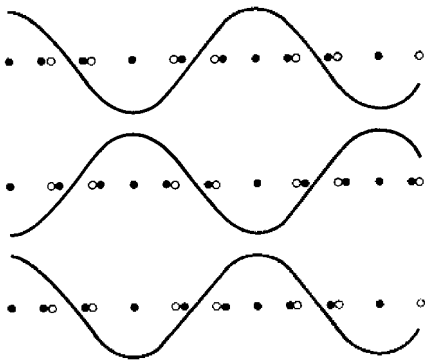


Figure 2 Peierls distortion of 1D atom chains. The diagram shows adjacent chains in the correlated state below T_{3D} (reproduced by permission from *Phys. Rep.*, 1978, **40**, 203)

In the PD state the electron density of the conduction band is perturbed by the displacement of the positive metal ions from their undistorted positions. This is known as a charge density wave (CDW). In a perfect 1D system a phase change can only occur at 0 K and it is through the presence of weak 3D effects that real compounds exhibit metal–semiconductor transitions at finite temperatures. In metal complexes the chains of metal atoms are surrounded by ligands, cations, water molecules and sometimes anions and these chemical species allow weak interchain interactions. These interactions are important in allowing coulombic interactions to become strong enough at low temperatures to cause 3D ordering of the CDWs on adjacent chains (Figure 2). The temperature at which this occurs is known as the three-dimensional ordering temperature, T_{3D}.

Experimentally the PD may be studied by diffuse X-ray scattering (DXS) experiments in which the 1D distortion of the chains gives rise to weak continuous lines on either side of the layer lines of strong Bragg spots.[10] The periodicity of the PD may be determined from the position of the diffuse line. In contrast, 3D superstructures give rise to real satellite reflections associated with the Bragg spots.

Metallic properties are also observed in columnar stacked complexes in which the intrachain separation is too long for conduction to be associated with the formation of a band from overlap of the metal d_{z^2}/p_z orbitals. For these complexes the conduction process involves carriers present in the delocalized MOs extending over the whole complex. The conduction process in these compounds may be described by a hopping mechanism in which the on-site Coulomb repulsion energy has been reduced by the delocalization of the charge over the whole molecule.

Although there has not been a review attempting to cover the whole field of conducting metal complexes, a number of books, conference proceedings and articles have appeared which contain discussions of the conduction properties associated with individual classes of compound.[11–24]

60.2 KROGMANN SALTS

Krogmann in a review article in 1969[23] opened up the new area of one-dimensional metals by his studies of partially oxidized platinum and iridium complexes. This type of compound had originally been discussed in the mid-19th century,[25] and again in the first part of the 20th century,[26] but it was not until the structural studies of Krogmann and coworkers that the true nature of these materials was understood. The compounds are based on square coplanar anions possessing a d^8 electronic configuration and are restricted to complexes of Pt or Ir with small ligands capable of π back-bonding with the central metal. The most commonly studied compounds are derived from $[Pt(CN)_4]^{2-}$ or $[Pt(C_2O_4)_2]^{2-}$, although some work has been carried out on systems based on $[Ir(CO)_2Cl_2]^-$.

The simple integral oxidation state compounds behave as either insulators or semiconductors. The tetracyanoplatinates of monovalent cations form anionic columnar stack structures with conductivities in the range 10^{-4}–10^{-9} Ω^{-1} cm^{-1} and a systematic variation of $\sigma_{\|}$ with $1/d_{Pt-Pt}$ has been observed.[6] The electrical conductivity can be increased by as much as a factor of 10^4 by pressures up to 180 kbar.[27]

The Krogmann salts are prepared by partial oxidation of the integral oxidation state compounds. Oxidation can be carried out either by chemical means (Cl_2, H_2O_2 or atmospheric O_2) or electrolytically. Details of the preparative details of many of these compounds have been published.[28] In many cases high quality single crystals can be obtained suitable for solid state studies.

There are basically two different types of Krogmann salts. (a) The anion-deficient (AD) salts. In these salts the additional positive charge on the Pt atoms due to partial oxidation is compensated for by the incorporation of a non-stoichiometric number of anions compared with the parent complex. For example, in the tetracyanoplatinate series the salts have the general formula $M_2[Pt(CN)_4]X_n{\cdot}pH_2O$ (where M is a monovalent cation, X an anion, and n a non-integer (0.19 to 0.49)). (b) Cation-deficient (CD) salts. In these salts a non-stoichiometric deficiency of cations compared with the parent Pt^{II} complex compensates for the partial oxidation of the platinum atoms. The general formula is, therefore, $M_m[PtL_4]{\cdot}pH_2O$ (where m is a non-integer and L is CN or $\frac{1}{2}(C_2O_4)$).

60.2.1 Tetracyanoplatinates (tcp)[22,24,29]

60.2.1.1 Anion-deficient salts

The ADtcp complexes are the most extensively studied series of Krogmann salts. In particular, the solid state properties of $K_2[Pt(CN)_4]Br_{0.30}{\cdot}3.2H_2O$, KCP(Br), have been studied in great detail because of the availability of large high quality single crystals.[30–32]

In KCP(Br) the DPO indicates that 0.30 electrons per platinum atom have been removed from the highest filled band (predominantly $5d_{z^2}$) to leave 1.70 electrons per platinum atom in the band. The structure of KCP(Br) contains columnar stacks of $[Pt(CN)_4]^{1.7-}$ ions with a linear Pt atom chain aligned along the c axis of the unit cell (Figure 3).[33] The d_{Pt-Pt} is 2.89 Å, which is only slightly longer than that observed in Pt metal (2.774 Å). The interchain Pt—Pt distance is 9.89 Å. The Br^- ions are located at the centre of the unit cell but only 60% of the available crystallographic sites are occupied by Br^- and the 3D random occupation of these sites leads to a random electrostatic potential along the chain axis. The unit cells which do not contain a Br^- in the centre contain an additional water molecule. The K^+ ions are located in one half of the unit cell whilst the remaining water molecules occupy the other half. The water molecules form a hydrogen-bonded network between the cyanide ligands and either the bromide ion at the centre of the unit cell, or the cyanide group of a $[Pt(CN)_4]^{1.7-}$ ion in an adjacent chain. Classical structural studies show that apart from a reduction in the unit cell dimensions there is no marked change in the structure on cooling to 31 K.[33]

Extensive studies of the temperature dependence of the PD have been made by DXS and neutron scattering experiments.[34–36] The PD at room temperature is incommensurate with the basic lattice with a repeat distance of 6.67 d_{Pt-Pt}. At room temperature there is little correlation between the chains whereas at 37 K the PD/CDWs are partially ordered in three dimensions. At 80 K the correlation length along the chains is over 100 Pt atoms whereas the interchain correlation length is only about five interchain spacings.[35]

The temperature dependence of the electrical conductivity of KCP(Br) has been studied by Zeller and Beck (Figure 4).[37] At room temperature, $\sigma_{\|}$ is about 300 Ω^{-1} cm^{-1} and the dependence of conductivity on temperature is slightly negative with the degree of anisotropy $\sigma_{\|}/\sigma_{\perp}$ of about 10^5.

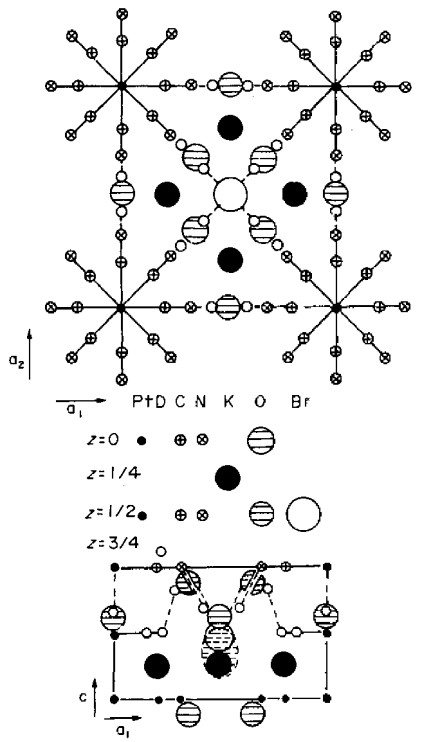


Figure 3 The unit cell of $K_2[Pt(CN)_4]Br_{0.30}\cdot 3.2H_2O$ projected along the *c* and *b* axes (reproduced by permission from *Phys. Rep.*, 1978, **40**, 204)

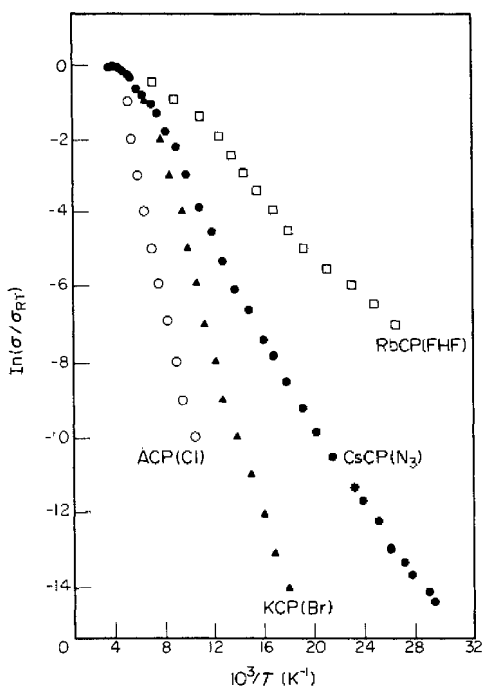


Figure 4 Variation of $\ln(\sigma/\sigma_{RT})$ versus $1/T$ for ACP(Cl) (open circles), KCP(Br) (triangles), $CsCP(N_3)$ (closed circles) and RbCP(FHF) (open squares) (reproduced by permission from *Phys. Rev. Lett.*, 1981, **47**, 1220)

On lowering the temperature the conductivity passes through a maximum and then follows a complicated temperature dependence. The first partial derivative of $\ln \sigma_{\parallel}$ with respect to $1/T$ has a maximum at 100 K, corresponding to the partial 3D ordering temperature, T_{3D}, found from neutron diffraction studies. At low temperature the behaviour is that of a semiconductor with a well-defined band gap. Studies at microwave frequencies have shown that the conductivity is frequency dependent below T_{3D}.[38] Studies under pressure indicate that T_{3D} increases and T_p decreases with increasing pressure, suggesting that the PD might be suppressed at pressures greater

than 70 kbar.[39] An alternative explanation of the metal–non-metal transition in KCP(Br) has been proposed in which a mixed valence state of $0.85Pt^{II}$ and $0.15Pt^{IV}$ is the ground state, and a Pt^{III} state an excited state.[40]

Following the discovery of the 1D metallic properties of KCP(Br), a whole series of ADtcps have been prepared and their structures and electrical conduction properties studied (see Table 1 and Figure 4). A number of these compounds are isostructural with KCP(Br) whilst others have a somewhat similar structure but are anhydrous. The variation in electrical conduction and solid state properties with changes in the structure and chemical composition of the lattice for this series of ADtcps is now well understood.[29] The conductivity at room temperature is very dependent on the intrachain Pt—Pt distance, varying from over $10^3\ \Omega^{-1}\ cm^{-1}$ for the FHF salt with a d_{Pt-Pt} of 2.798 Å, and dropping to $0.4\ \Omega^{-1}\ cm^{-1}$ for the NH_4^+ salt with an average d_{Pt-Pt} of about 2.92 Å. This variation is clearly related to the extent of orbital overlap and hence to the width of the conduction band. As first pointed out by Williams, there is a close relationship between the d_{Pt-Pt} and DPO.[60] Hence there is also a relationship between the d_{Pt-Pt} and the extent of band filling and the value of the Fermi wave-vector k_F. Since optical studies have shown the conduction electrons in KCP(Br) exhibit free-electron like behaviour, the solid state properties of this series of compounds have been discussed using the free-electron approximation.[61] This has enabled the calculation of the dimensionless electron–phonon coupling constant, λ, from the observed value of Δ at low temperatures. There is a regular variation of both Δ and λ with d_{Pt-Pt} and hence DPO. The value of T_{3D} has been found to be strongly dependent upon the presence of hydrogen-bonding between the chains. Thus the hydrated compounds have higher values of T_{3D} than the anhydrous compounds and ACP(Cl), in which the NH_4^+ ions can form an additional hydrogen-bonded network between the platinum atom chains, exhibits a much higher value than any of the other compounds.[61] A series of compounds based on POtcp containing both monovalent and divalent cations has been described.[51] The introduction of divalent in place of monovalent cations in the KCP structure was shown to have a large effect on the conduction properties due to the increased stiffness of the lattice.[51]

Table 1 Partially Oxidized Tetracyanoplatinate Salts

Compound	*Abbreviation*	*Space group*	d_{Pt-Pt} (Å)	$\sigma_{\parallel}$ ($\Omega^{-1}\ cm^{-1}$)	Δ (meV)	k_F ($\pi/d_{Pt\cdots Pt}$)	λ	T_{3D} (K)	*Ref.*
Pt	—	—	2.775	9.4×10^4	—	—	—	—	
$Rb[Pt(CN)_4](FHF)_{0.40}$	$RbCP(FHF)_{0.4}$	*I4/mcm*	2.798(1)	2.3×10^3	≈18	0.80	0.20	80	41[s],42[c]
$Rb_3(H_3O)_{0.2}[Pt(CN)_4]\cdot(O_3SO{\cdot}H{\cdot}OSO_3)_{0.5}\cdot0.8H_2O$	RbCP(DSH)	$P\bar{1}$	2.826(1)	4×10^2	43	0.85	0.25	⩽80	43
$Cs_2[Pt(CN)_4](FHF)_{0.39}$	$CsCP(FHF)_{0.4}$	*I4/mcm*	2.833(1)	2×10^3	27	0.80	0.22	80	44[s],42[c]
$Cs_2[Pt(CN)_4]Cl_{0.3}$	CsCP(Cl)	*I4/mcm*	2.859(2)	2×10^2	30	0.85	0.23	90	45[s],46[c]
$Cs_2[Pt(CN)_4](FHF)_{0.23}$	$CsCP(FHF)_{0.23}$	*I4/mcm*	2.872(2)	2×10^2	—	—	—	—	29[s]
$K_2[Pt(CN)_4]Cl_{0.32}\cdot3H_2O$	KCP(Cl)	*P4mm*	2.874	2×10^2	70	0.84	0.29	95	47[s],48[c]
$Cs_2[Pt(CN)_4](N_3)_{0.25}\cdot0.5H_2O$	$CsCP(N_3)$	$P\bar{4}\,b2$	2.877(1)	1.5×10^2	41	0.875	0.26	110	49[s],50[c]
$Cs_2[Pt(CN)_4]F_{0.19}$	CsCP(F)	*Immm*	2.886(1)	—	—	—	—	—	29[s]
$K_2[Pt(CN)_4]Br_{0.3}\cdot3.2H_2O$	KCP(Br)	*P4mm*	2.888	2×10^2	72	0.85	0.30	100	33[s],37[c]
$Rb_2[Pt(CN)_4](FHF)_{0.26}\cdot1.7H_2O$	$RbCP(FHF)_{0.26}$	*C2/c*	2.89	—	—	—	—	—	29[s]
$Pb_{0.27}K_{1.73}[Pt(CN)_4]Cl_{0.5}\cdot3H_2O$	Pb/KCP(Cl)		2.899	10^2	27	0.885	0.29	≈85	51
$Rb_2[Pt(CN)_4]Cl_{0.3}\cdot3H_2O$	RbCP(Cl)	*P4mm*	2.877(8), 2.924(8)	10	75	0.845	0.30	110	52[s],48[c]
$[C(NH_2)_3]_2[Pt(CN)_4]\cdot(FHF)_{0.26}\cdot xH_2O$	$GCP(FHF)_{0.26}$		2.90	—	—	—	—	—	53[s]
$[C(NH_2)_3]_2[Pt(CN)_4]Br_{0.25}\cdot H_2O$	GCP(Br)	*I4cm*	2.908(2)	11	45	0.875	0.27	100	54
$(NH_4)_2(H_3O)_{0.17}[Pt(CN)_4]\cdot Cl_{0.42}\cdot2.8H_2O$	ACP(Cl)	*P4mm*	2.910(5), 2.930(5)	0.4	125	0.875	0.38	195	55[s],56[c]
$K_{1.75}[Pt(CN)_4]\cdot1.5H_2O$	KCP(def)	—	2.963	50	—	0.875	—	—	57[s,c],58[s], 59[s]

[s] structure
[c] conductivity.

60.2.1.2 Cation-deficient salts

A series of salts $M_{1.75}[Pt(CN)_4]\cdot1.5H_2O$ (where M is K, Rb or Cs) has been reported but only the K salt has been studied in detail. The DPO for this salt is 0.25 and, therefore, the PD will have a repeat distance of eight d_{Pt-Pt} and this would be expected to lead to a crystal structure with an eight-fold superlattice repeat distance. Structural studies have shown that above about 294 K the unit cell contains four $[Pt(CN)_4]^{1.75-}$ ions with a zig-zag Pt atom chain.[58] Below 294 K a phase transition occurs to give a new unit cell with a repeat distance in the Pt atom chain direction which

is the same as the PD/CDW.[59] The temperature dependence of $\sigma_{\parallel}$ in this salt is well established but the behaviour has been the subject of conflicting explanations. The recent structural studies indicate that the transition at 294 K can be regarded as a $2k_F-4k_F$ transition.[57] A new type of CD salt involving both mono- and di-valent cations, $Pb_{0.77}K_{0.23}[Pt(CN)_4]\cdot 1.5H_2O$, has also been studied.[62]

60.2.2 Bis(oxalato)platinates

1D metals based on the $[Pt(C_2O_4)_2]$ anions are all of the cation-deficient type. Unlike the tcps they are found with either mono- or di-valent cations. A comprehensive review of the literature up to 1979 has been published and is a source of earlier references.[63] Details of well-characterized compounds are given in Table 2.

Table 2 Partially Oxidized Bis(oxalato)platinate Salts

Compound	*Abbreviation*	*Intrachain Pt—Pt separation* (Å)	*DC studies* $\sigma_{\parallel}$[a] (Ω^{-1} cm^{-1})	*DC studies* E[a] (meV)	*35 GHz studies*[157] $\sigma_{\parallel}$[a] (Ω^{-1} cm^{-1})	*35 GHz studies*[157] $\sigma_{\perp}$[a] (Ω^{-1} cm^{-1})	*Ref.*
$K_{1.62}[Pt(C_2O_4)_2]\cdot 2H_2O$	α-KOP	2.82	10^2 (max)	10 (< 190 K)	—	—	57[s]
$K_{1.81}[Pt(C_2O_4)_2]\cdot 2H_2O$	γ-KOP	2.837	10 (max)	15 (< 170 K)	—	—	64[s], 65[c]
$Rb_{1.67}[Pt(C_2O_4)_2]\cdot 1.5H_2O$	α-RbOP	2.717 2.830 3.015	7×10^{-3}	77	—	—	66, 57[s,c]
$[H_3NCH_2CH_2NH_3]_{0.82}[Pt(C_2O_4)_2]\cdot 2H_2O$	enH_2OP	2.832	4	50–59 (< 250 K)	—	—	67[c]
$Mg_{0.82}[Pt(C_2O_4)_2]\cdot 5.3H_2O$	MgOP	2.86	50 (max)	85	34 (max)	10^{-1} (max)	69[s], 70[c], 68[s], 72[T], 71[c,R], 75[c]
$Co_{0.83}[Pt(C_2O_4)_2]\cdot 6H_2O$	CoOP	2.841	25 (max)	50 (< 250 K)	38 (max)	4×10^{-1} (max)	73[s], 74[c,s], 75[c], 72[T]
$Mn_{0.81}[Pt(C_2O_4)_2]\cdot 6H_2O$	MnOP	2.835	47 (max)	55 (< 110 K)	—	—	72[c], 71[c]
$Zn_{0.81}[Pt(C_2O_4)_2]\cdot 6H_2O$	ZnOP	2.838	94 (max)	54 (< 250 K)	—	—	76[c,R], 77[s]
$Cu_{0.84}[Pt(C_2O_4)_2]\cdot 7H_2O$	CuOP	2.876	10 (max)	—	6 (max)	6×10^{-3} (max)	63, 75[c]
$Fe_{0.8}[Pt(C_2O_4)_2]\cdot 6H_2O$	FeOP	—	—	—	—	—	78
$Ni_{0.84}[Pt(C_2O_4)_2]\cdot 6H_2O$	NiOP	2.835	22 (max)	58 (< 275 K)	—	—	72[c,T], 79[s]

[s] structure
[c] conductivity
[R] reflectivity
[T] thermopower.

60.2.2.1 Monovalent cation salts

The partially oxidized bis(oxalato)platinate salts of monovalent cations are often characterized by the existence of several crystalline phases each with very similar stoichiometry. This is particularly true for the potassium salts. Four crystalline phases of stoichiometry $K_{1.6\pm0.04}[Pt(C_2O_4)_2]\cdot xH_2O$ (α-, β-, δ- and ε-KOP) are known plus $K_{1.81}[Pt(C_2O_4)_2]\cdot 2H_2O$ (γ-KOP).[63]

The most studied potassium salt is γ-KOP. The fundamental structure of this compound consists of four planar $[Pt(C_2O_4)_2]^{1.81}$ units stacked along the *b* axis of the crystal to form zig-zag chains. The crystals also show characteristic X-ray satellite reflections indicating a sinusoidally-modulated lattice at room temperature.[64] The component of the wave-vector of the modulation wave in the platinum atom chain direction is $0.38b^*$, indicating a period of 29.92 Å. However, unlike KCP(Br), below 100 K the modulation wave in γ-KOP has both longitudinal and transverse components. The amplitude of the modulation wave at 298 K is about 0.17 Å, which is about seven times greater than that found in KCP(Br) at liquid He temperature. There is excellent agreement between the $2k_F$ value deduced from the chemical analysis and the wave number determined by the X-ray diffraction experiments, confirming that the modulated superstructure arises from the condensation of the $2k_F$ phonons. The room temperature conductivity, $\sigma_{300\,K}$, is $10\,\Omega^{-1}$ cm^{-1} and the crystals behave as semiconductors below room temperature.[57,65]

The rubidium salt $Rb_{1.67}[Pt(C_2O_4)_2]\cdot 1.5H_2O$ (RbOP) is a compound exhibiting a commensurate $2k_F$ structure and, therefore, the distortion of the Pt chain has been determined precisely.[66] The unit cell contains a distorted nonlinear sixfold Pt atom chain and involves six $[Pt(C_2O_4)_2]^{1.67-}$ units in one repeating unit of 17.11 Å. There are three independent Pt—Pt distances of 2.716, 2.830 and 3.015 Å. The Pt—Pt distance of 2.717 Å is the shortest spacing so far observed in partially oxidized platinum complexes and it is shorter than the 2.77 Å interatomic distance in Pt metal.

The differences in the platinum–platinum distances in α-RbOP are much greater than those in α-KOP. In α-RbOP the oxalate ligands are staggered with respect to the ligands on adjacent platinum atoms in the chain with torsion angles of about 46°, 55° and 80°, while alternate ligands are eclipsed or staggered by about 90°. Owing to electrostatic interaction between Rb^+ and H_2O and the nonbonded oxygen atoms of the ligands, the oxalate ligands are not exactly planar. The five independent Rb ions all occupy general positions in the space group and are approximately located with the water molecules in layers parallel to the platinum atom chains. The characteristic deformation of the $[Pt(C_2O_4)_2]$ units has been interpreted as showing that the gain of the electronic energy obtained from the $2k_F$ distortion of the Pt chains must be larger than the sum of the molecular deformation energy and the lattice distortion energy.[57] In this case, the displacement reactors of the atoms cannot be described precisely in terms of a simple sinusoidal wave. α-RbOP behaves as a semiconductor from 305 to 83 K with an activation energy of 77 meV. The low value of the room temperature conductivity, $7 \times 10^{-3}\ \Omega^{-1}\ cm^{-1}$, can be ascribed to the very disparate intrachain Pt—Pt separations. Studies have also been made of the electrical conduction properties of partially oxidized bis(oxalato)platinate salts of ammonium and methyl substituted ammonium cations.[80]

60.2.2.2 Divalent cation salts

A large number of partially oxidized divalent cation salts of the bis(oxalato)platinates have been reported (see Table 2).[63] Only the series $M_x[Pt(C_2O_4)]\cdot 6H_2O$ (MOP where M = Fe, Co, Ni, Zn, Mg and $0.80 < x < 0.85$) has been extensively studied.[68–83] For most of these salts detailed studies have been made of their crystal structures and optical reflectivity at room temperature, and the variation of superlattice reflections, diffuse X-ray scattering, thermopower and DC electrical conductivity with temperature.

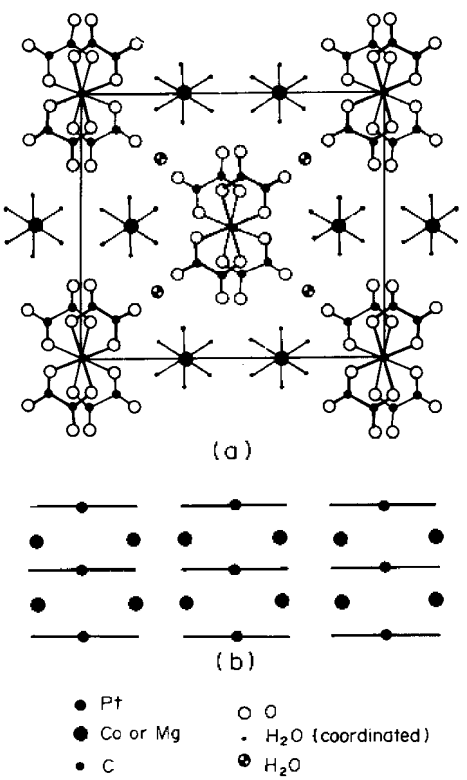


Figure 5 Crystal structure of CoOP: (a) projection parallel to Pt atom chains; (b) projection perpendicular to Pt atom chain (reproduced by permission from 'Molecular Metals', ed. W. E. Hatfield, NATO Conference Series VI, Materials Science, Plenum, New York, 1979, vol. 1, p. 378)

Both CoOP and MgOP exist in the same orthorhombic structure with space group *Cccm* at an appropriately high temperature with little variation in unit cell dimensions.[68,73] This structure for CoOP is shown in Figure 5 and contains linear chains of $[Pt(C_2O_4)_2]^{x-}$ units with d_{Pt-Pt} of 2.85 Å in the Mg^{2+} and 2.841 Å in the Co^{2+} salts.[73] The divalent metal ions are located between the planes containing the bis(oxalato)platinate ions and are coordinated to six water molecules with

a slightly distorted octahedral geometry. There are eight sites for the hydrated metal ions and 41% of these are randomly occupied in three dimensions. The water molecules form a hydrogen-bonded network crosslinking the bis(oxalato)platinate anions *via* the divalent metal atoms. Additional water molecules lie outside the coordination sphere of the M^{2+} ion but hydrogen-bonded to coordinated water molecules.[73]

The crystal structure of $Ni_{0.8}[Pt(C_2O_4)_2]\cdot 6H_2O$, NiOP, has been determined at room temperature and shown to belong to the space group *Pccn*.[79] The structure is very similar to that of CoOP and MgOP at room temperature except that the Pt atom chains are not equivalent. The change in space group results from the $[Pt(C_2O_4)_2]$ anion chain in the centre of the unit cell slipping by 0.15 Å compared with the $[Pt(C_2O_4)_2]$ chains at the corners of the unit cell.

A characteristic feature of these partially oxidized bis(oxalato)platinate salts of divalent cations is the coexistence of two modulations of the lattice over a wide temperature range: (a) a one-dimensional modulation, as detected by the appearance of diffuse lines on X-ray films, perpendicular to the $[Pt(C_2O_4)_2]$ anion stacking direction and surrounding the even Bragg reflection layer lines of non-zero order; (b) a three-dimensional modulation which gives rise to a complicated pattern of fine satellite spots in the neighbourhood of every reciprocal layer line.

These salts exhibit complicated phase transitions which have a profound effect on their electrical conduction properties. It is only very recently that many of these features have been studied.

In CoOP above 300 K the compound exists in the *Cccm* space group, but with characteristic diffuse X-ray lines indicative of the Peierls modulation and no evidence of superstructure formation. Below 300 K a superstructure develops as shown by the appearance of satellite reflections on the X-ray diffraction photographs. At 280 K a phase transition to the *Pccn* space group occurs and associated with this are changes in the satellite pattern.[78,74] Superstructure development which is commensurate with the Peierls modulation is completed about 250 K.

The electrical conductivity of CoOP as a function of temperature is shown in Figure 6. Above room temperature the compound exhibits metallic behaviour but coincidental with the development of the superstructure the conductivity falls rapidly with decreasing temperature. Below 250 K CoOp behaves as a semiconductor with an activation energy of meV.[74] The conduction has been shown to be frequency dependent below 250 K.[75] Thermopower studies have also clearly demonstrated the changeover from metallic behaviour above 300 K to semiconductor behaviour below 250 K.[72] The behaviour of ZnOP is very similar to that of CoOp, with the phase transition from the *Cccm* to *Pccn* space group occurring at 278 K. Superstructure formation is complete by about 260 K.[77]

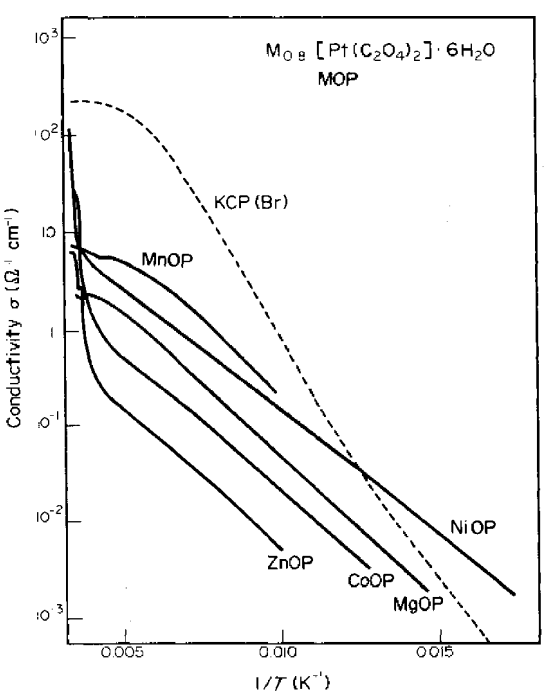


Figure 6 Variation of electrical conductivity with inverse temperature for a series of bis(oxalato)platinate salts

NiOP already exists in the *Pccn* group at room temperature and weak diffuse X-ray scattering and k_F and $2k_F$ satellite reflections are observed.[79] The $2k_F$ spots disappear above 305 K and the conductivity is similar to that observed for CoOP and ZnOP.[79,72]

Although MgOP and CoOP are isostructural above 290 K, their behaviours below this temperature are very different. MgOP undergoes an orthorhombic to twinned monoclinic phase transition at about 283 K, in which the Pt atom chain tilts by 1° towards the *b* axis.[69] This does not result in any significant change in either the interchain Pt—Pt separation or in the interchain distance. In fully hydrated crystals the phase transition is also accompanied by the development of satellite spots, indicating the formation of a superstructure. The position of the spots indicates a three-dimensional modulation of the platinum atom chain giving rise to a superlattice with unit-cell dimensions (*a*, 6.5*b*, 5.3*c*). A diffuse X-ray line due to the period of the Peierls modulation of the platinum atom chain and corresponding to a repeat distance along *c* of 3.2*c* has also been observed in MgOP at room temperature. Thus the periods of the Peierls modulation and the 3D modulation appear to be incommensurate in MgOP, although they are commensurate in CoOP, ZnOP and NiOP.

The electrical conduction and thermopower properties of MgOP are quite different from those of the Co, Zn and Ni salts.[70–72] At the phase transition there is an increase in conductivity of about 10% on going from the high-temperature orthorhombic to the low-temperature monoclinic phase in MgOP, but changes by a factor of up to ten were observed for the other salts. Whereas the changes in conductivity were spread over 30–50 degrees for CoOP, NiOP and ZnOP, the transition occurs over a temperature range of only a few degrees in MgOP. Time-dependent changes in conductivity and thermopower at a constant temperature were observed during the phase change in MgOP at timescales of several hours, whereas no such observations were made with the other salts.[70,71]

The iron(II) salt at room temperature is isomorphous with CoOP but undergoes a transition to the same twinned monoclinic structure with accompanying superstructure exhibited by MgOP.[78] The solid state properties of this salt have not been studied in detail. MnOP also exists in the twinned monoclinic form at room temperature. However, the conductivity and thermopower properties as a function of temperature are very different from those of MgOP.[72,71] The electrical conduction studies of MnOP show a transition at 225 K, which corresponds to a change in the thermopower from metallic to semiconducting properties.[72] A second transition can be observed at 120 K from the conductivity data but this has only a minor effect on the thermopower.[71] Studies on compressed pellets of $Pb_{0.8}[Pt(C_2O_4)_2]\cdot nH_2O$ and $Cd_{0.8}[Pt(C_2O_4)_2]\cdot nH_2O$ have been reported.[81]

Two models have been developed to describe the superstructure found in these salts. In the Kobayashi *et al.* model, cation ordering in the channels adjacent to the $[Pt(C_2O_4)_2]$ chain is responsible for the development of the superstructure and the 3D modulation of the Pt atom chain.[79] On the other hand, Bertinotti and coworkers have proposed that the chains are fragmented into micro-domains by periodic intrinsic defects associated with polarons.[78,82] Three orthogonal deformation modes, one longitudinal and two transverse, are present in each chain and a fourth mode corresponds to a global sliding of the molecular column.

As can be seen from the above discussions, the electrical conduction properties of these compounds are strongly affected by the phase changes and superstructure development observed from X-ray studies. The anomolous behaviour of MgOP has been ascribed to chaos arising from competition between instabilities.[83] The interdependence of these, however, is not simple, and a full understanding of these systems is not available.

Partially oxidized bis(squarato)platinum and bis(croconato)platinum salts have been reported but detailed studies have been restricted by the lack of suitable single crystals.[84]

60.2.3 Dihalodicarbonyliridates[85]

The reaction of K_2IrCl_6 with CO under pressure at 170 °C produces a material of gold appearance, which can be recrystallized from acetone solution to yield very fine needle-like golden crystals of variable stoichiometry $K[Ir(CO)_2Cl_x]$ ($x = 2.3–2.7$). Cleare and Griffith showed that a series of compounds $Y[Ir_2(CO)_4X_4]$, where $Y = K^+$, Cs^+, Ph_4As^+ or Bu_4N^+ and $X = Cl^-$ or Br^-, could be readily prepared from the reaction of $[IrX_6]^{3-}$ with formic and hydrohalogenic acids.[86] However, these materials are unstable and do not readily form single crystals and this has severely restricted both the chemical and physical characterization of these materials. In particular, the stoichiometry of many of these compounds is controversial and non-reproducible and as yet no complete three-dimensional structure determination has been completed. The chemical stability of the compounds decreases in the order chloro > bromo > iodo.

Krogmann and Geserich showed these compounds to be linear metal atom chain compounds with short intrachain Ir—Ir separations of 2.86 Å, and that they have related structures to the cation-deficient bis(oxalato)platinates.[87] A detailed study of these compounds showed that the

needle crystals are strongly dichroic, exhibiting a metallic lustre in reflected light.[88] The oxidation state of the iridium ranges from 1.39 to 1.44 and Mössbauer studies show that all the Ir atoms are equivalent. The variation of stoichiometry observed by different workers probably arises from the presence of alkali halides as interstitial precipitates in the lattice and, therefore, material such as $Na_{0.93}Ir(CO)_2Cl_{2.32}$ should be formulated as $Na_{0.61}[Ir(CO)_2Cl_2]\cdot 0.32NaCl$.[88]

The electrical conductivity of several of these compounds has been reported.[88] Compressed pellet four-probe measurements at room temperature are usually in the range 10^{-2}–5 Ω^{-1} cm^{-1} although a value of 150–500 has been reported for orientated polycrystals. Most of the compounds show semiconductor behaviour with activation energies of about 35 meV. $K_{0.60}[Ir(CO)_2Cl_2]\cdot 0.5H_2O$ shows evidence of a transition to more metal-like behaviour near room temperature.[88] It seems very likely that if good quality single crystals of these compounds could be obtained then they would exhibit conduction properties similar to those of the cation-deficient tetracyanoplatinates or bis(oxalato)platinates.

60.3 NEUTRAL COMPLEXES AND DERIVATIVES

Neutral square coplanar complexes of divalent transition metal ions and monoanionic chelate or dianionic tetrachelate ligands have been widely studied. Columnar stack structures are common but electrical conductivities in the metal atom chain direction are very low and the temperature dependence is that of a semiconductor or insulator. However, many of these compounds have been shown to undergo partial oxidation when heated with iodine or sometimes bromine. The resulting crystals exhibit high conductivities occasionally with a metallic-type temperature dependence. The electron transport mechanism may be located either on predominantly metal orbitals, predominantly ligand π-orbitals and occasionally on both metal and ligand orbitals. Recent review articles deal with the structures and properties of this class of compound in detail.[89,90,12]

60.3.1 α,β-Dionedioximates

Square coplanar complexes of the nickel triad with dimethylglyoxime (DMG), diphenylglyoxime (DPG) and benzoquinone dioxime (BQD) have been extensively studied (see Figure 7). There are two basic structural motifs. The Type A structure as typified by α-$Pd(BQD)_2$ contains the planar units stacked in columns with the M—M vector parallel to the stacking axis and usually with a repeat distance of 2 units.[91] The M—M distance is short (3.15–3.40 Å) and the packing inefficient, leading to the existence of channels in the stacking direction. Some evidence of anisotropic properties has been observed.[92] In the Type B structure as shown by $Ni(BQD)_2$[93] the planar units are in a slipped stack arrangement so that the M—M vector is not parallel to the stacking direction. This results in a large M—M distance but more efficient packing and often a herringbone arrangement. All these compounds exhibit semiconductor behaviour with very low conductivities at room temperatures in the metal atom chain direction.[89] Under high pressure, $Pt(DMG)_2$ has a conductivity of 10 Ω^{-1} cm^{-1} (40 kbar).[94]

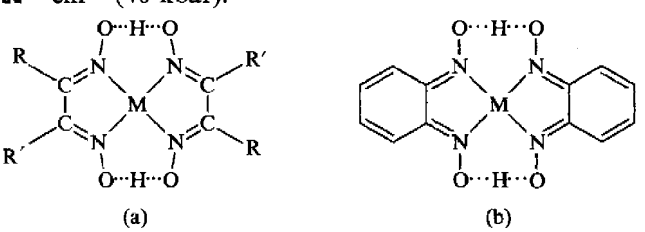


Figure 7 α, β-Dionedioximates: (a) R = R′ = Me, dimethylglyoxime (DMG); R = R′ = Ph, diphenylglyoxime (DPG); (b) benzoquinone dioxime (BQD)

60.3.1.1 Non-integral oxidation state compounds

Conducting halogenated linear metal atom chain systems were first reported in 1950[95] and are now known for Ni and/or Pd complexes of glyoxime (GLY), DPG and BQD. The compounds are usually produced by treating a hot solution of the neutral complex in *o*-$C_6H_4Cl_2$ with I_2 and lustrous coloured crystals of the NIOS compound are obtained on cooling the solution. The limited range of compounds studied is shown in Table 3 and all have metal-over-metal stacked structures.

A complete 3D structure of $Ni(DPG)_2I$ has been published and this shows a tetragonal space group with stacks of $Ni(DPG)_2$ units staggered by 90°. The iodine species are located in channels parallel to the $Ni(DPG)_2$ stacks.[97] The presence of I_5^- ions has been identified from resonance

Table 3 Non-integral Oxidation State Metal Glyoximates and Benzoquinone Dioximates

Compound	d_{M-M} (Å)	*DC conditions* (Ω^{-1} cm^{-1})	Δ (eV)	*Ref.*
$Pd(GLY)_2I$	3.244(1)	—	—	96[s]
$Ni(DPG)_2I$	3.223(2)	$(2.3-1) \times 10^{-3}$	0.19 ± 0.001	97[s,c],98[c]
$Ni(DPG)_2Br$	3.271(1)	1.8×10^{-3}	0.22	98[c],53[s]
$Pd(DPG)_2I$	3.26(1)	$(7.7-47) \times 10^{-5}$	0.54 ± 0.11	98[s],97[c]
$Pd(DPG)_2Br_{1.1}$	3.27(1)	$(8.9-13) \times 10^{-5}$	0.23 ± 0.01	98[s,c]
$Ni(BDQ)_2I_{0.018}$	3.180(2)	$<9 \times 10^{-9}$	—	99[s,c]
$Ni(BDQ)_2I_{0.52} \cdot 0.32C_6H_5CH_3$	3.153(3)	$(1.8-11) \times 10^{-6}$	0.54 ± 0.008	99[s,c],100[s],92
$Pd(BDQ)_2I_{0.5} \cdot 0.520C_6H_4CH$	3.184(3)	$(7.8-810) \times 10^{-5}$	0.22 ± 0.03	99[s,c],92

[s] structure
[c] conductivity.

Raman and Mössbauer studies.[97] Thus the compounds are partially oxidized and should be more correctly expressed as $[M(DPG)_2](I_5)_{0.2}$ with the nickel in a formal oxidation state of 2.20.[97] The electrical conductivity in the Ni atom chain direction is 10^{-2} Ω^{-1} cm^{-1}, 10^5 times that of the unoxidized parent compound.[97,98] The temperature dependence of the conductivity indicates that the compound is a semiconductor with $\Delta E = 0.19 \pm 0.01$ eV. Table 3 indicates that changing the halide has little effect on the conductivity but that the Ni complex is more conducting than the Pd analogue.

An X-ray photoelectron spectroscopic study of $Ni(DPG)_2I$ showed no evidence of trapped valence or any appreciable change in the charge on the metal upon oxidation.[97] The site of partial oxidation and hence the electron transport mechanism is still unclear but one explanation of the relatively low conductivity is that the conduction pathway is metal centred and that the M—M distances are too long for effective orbital overlap. Electron transport could be *via* a phonon-assisted hopping mechanism or, in the Epstein–Conwell description, involve weakly localized electronic states, a band gap (2Δ) and an activated carrier concentration.[101]

The structures of the $M(BQD)_2I_{0.5}$ (M = Ni or Pd) complexes contain stacks of partially staggered $M(BQD)_2$ units and parallel chains of iodine atoms.[99,100] Unlike the $M(DPG)_2X$ structure there are two crystallographically distinct channels that are parallel to the $M(BQD)_2$ stacks and only the smaller diameter channel is occupied by iodine atoms. The large channel contains disordered solvent molecules. The iodine is present as I_3^- and hence the compounds should be written as $[M(BQD)_2^{+0.17}][I_3^-]_{0.17} \cdot xS$, with a degree of partial oxidation of 0.17. This is similar to the DPO of +0.20 observed in the $M(DPG)_2I$ compounds. Although M—M separation is less than in the $M(DPG)_2I$ counterparts, the thermally activated conductivity is also lower at 300 K with the Pd complex exhibiting a slightly higher conductivity than the Ni complex.[99]

60.3.2 Metalloporphyrins

The chemical flexibility of the porphyrin-like metallomacrocycles has been used to vary the electronic properties of the molecular units and hence the resulting solid. This has been brought about by the choice of the basic ligand, the peripheral substituents and the central metal. The main variants on the porphyrin skeleton are shown in Figure 8. A large number of compounds have been obtained as conducting polycrystalline powders by oxidation of the parent metallomacrocycle with iodine.[90] Table 4 contains details of compounds which have been obtained as single crystals and have been extensively characterized and studied.

Table 4 Non-integral Oxidation State Metallomacrocycles

Compound	d_{M-M} (Å)	*DC conditions* (Ω^{-1} cm^{-1})	T_m (K)	*Mean free path* (Å)	*Ref.*
$Ni(PC)(I_3)_{0.33}$	3.244(2)	260–750	55*	3.3–8.2	102
$Ni(TBP)(I_3)_{0.33}$	3.26(2)	34–150	95	2.2–4.1	103
$Ni(TATBP)(I_3)_{0.33}$	—	110–200	150	—	89
$Ni(OMTBP)(I_3)_{0.33}$	3.778(5)	4–16	300	1.6	105,106
$Ni(OMTBP)(I_3)_{0.97}$	—	1–4	340	—	105,106
$Ni(TMP)(I_3)_{0.33}$	3.466(3)	40–280	115	2.4–15	107

60.3.2.1 Nickel–iodine ligand complexes [Ni(L)I where L = PC, TBP or TATBP]

Iodine oxidation of Ni(PC), Ni(TBP) and Ni(TATBP) in each case yields crystals of composition Ni(L)I. Full X-ray diffraction, resonance Raman and ^{129}I Mössbauer studies show that the first

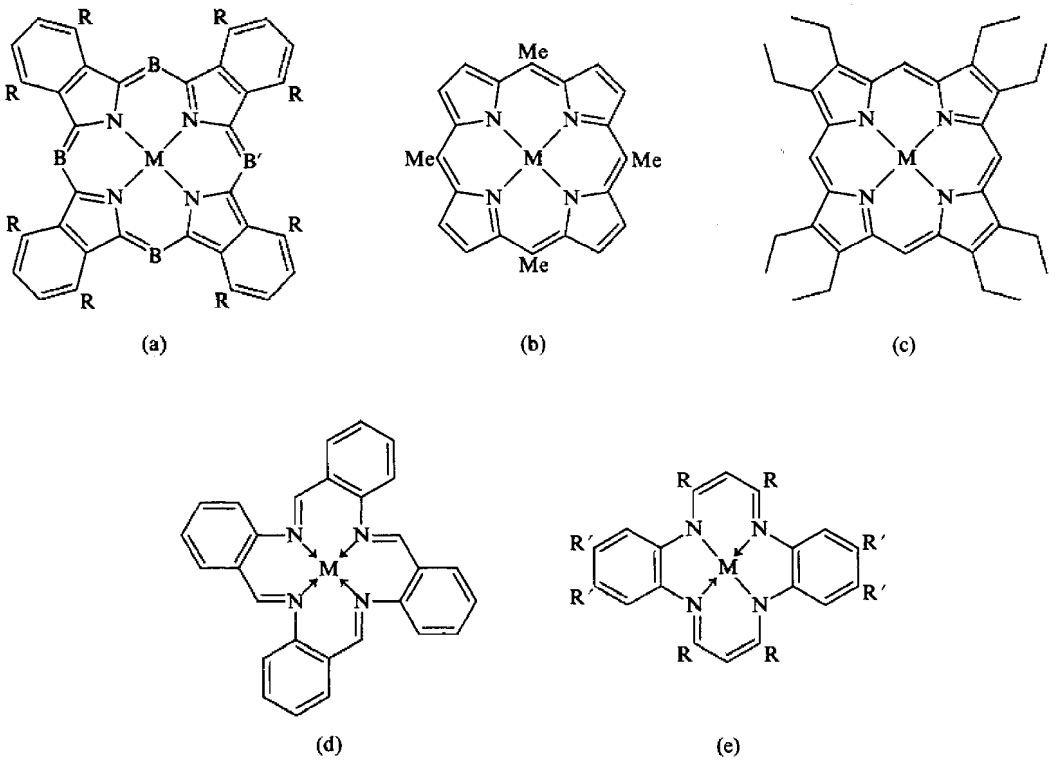


Figure 8 Metallomacrocycles: (a) R = H, B = B′ = N, M(PC); R = H, B = N, B′ = CH, M(TATBP); R = H, B = B′ = CH, M(TBP); R = Me, B = B′ = CH, M(OMTBP); (b) M(TMP); (c) M(OEP); (d) M(TAAB); (e) R = R′ = H (TAA), M = H_2, Co, Ni, Cu or Pd; R = H, R′ = Me (TMTAA), M = H_2, Ni or Pd; R = Me, R′ = H (TM′TAA), M = Ni

two compounds are isostructural and isomeric.[102,103] They contain columnar stacks of planar metallomacrocycles with parallel chains of I_3^- counter-ions (Figure 9). X-ray photographs suggest that Ni(TATBP)I has a similar structure.[89] In Ni(PC)I and Ni(TBP)I the iodine superlattice spacing is a multiple of the Bragg spacing so that the superlattice is commensurate with the Bragg lattice. The extent of I_3^- disorder is not severe and could be modelled satisfactorily.

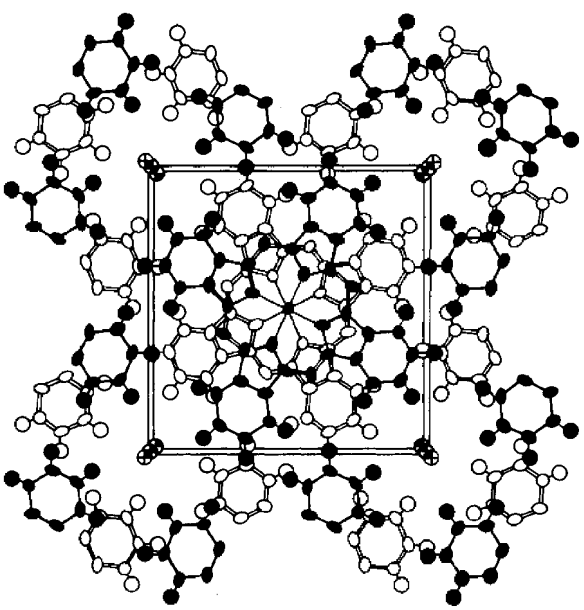


Figure 9 View down the *c* axis of the unit cell of Ni(PC)I (reproduced by permission from *Struct. Bonding (Berlin)*, 1982, **50**, 1)

Single crystals of all these compounds behave as molecular metals at room temperature, but the temperature dependence of the conductivities vary significantly from one another (Figure 10).

The room temperature conductivities and mean free paths for carrier motion along the stack are comparable with other 1D metals, including organic charge-transfer salts such as $(TTT)_2I_3$. The most striking feature is the abrupt metal to semiconductor transition observed for Ni(PC)I at approximately 60 K. There is no change in the resonance Raman spectra at the transition and therefore the extent of charge-transfer does not change. ESR studies indicate the presence of a ligand centred π-cation radical, suggesting that the 'hole-type carriers' are located on the ligand orbitals. Neither the temperature dependence of the ESR signal nor the weak paramagnetization, as detected by susceptibility measurements, is affected by the transition.[102] In Ni(TBP)I and Ni(TATBP)I the carrier spin *g*-value and line width are anomolous, and these results have been interpreted as indicating that these are the first partially oxidized complexes in which charge carriers exhibit both metal and ligand properties.[103,89] The electron 'hole' created by iodine oxidation is associated with both π and *d* 'bands' and can jump between the metal and the macrocyclic ligand as well as between one Ni(L) unit and its neighbours in the stack.[103]

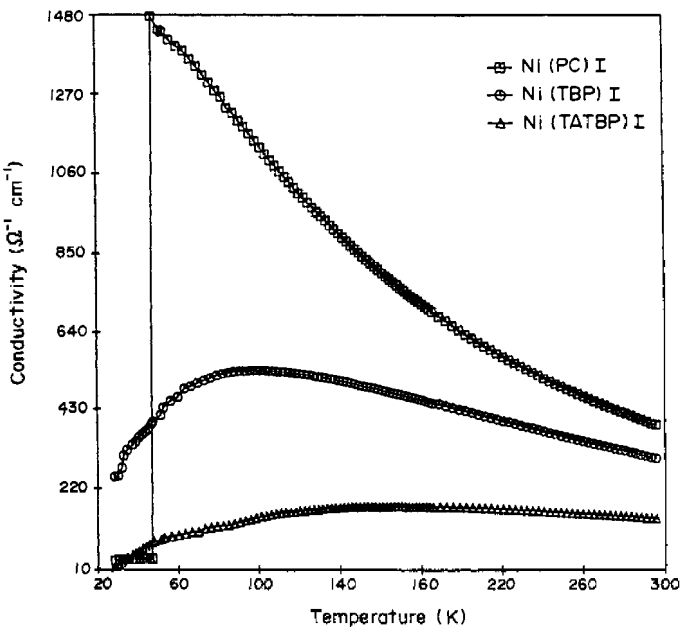


Figure 10 Temperature dependence of the conductivity for Ni(PC)I, Ni(TBP)I and Ni(TATP)I (reproduced with permission from *Struct. Bonding (Berlin)*, 1982, **50**, 1)

Recent band structure calculations have confirmed that the increase in electrical conductivity of doped polymer phthalocyanines is the result of both the existence of partially filled bands and the decrease of the M—M distance.[104] They also confirm that the conduction process for the doped polymers changes from metal-centred (M = Cr, Mn, Fe and Co), to ligand and metal (M = Ni) and to ligand-centred (Cu and Zn) with increasing electronegativity of the metal atom along the first transition series.

A range of compounds of the type $M(L)I_x$ (where L = PC, or a substituted PC, and M = Ni, Co, Cu or Pt and $0 < x < 5$) has been reported.[90] All the compounds have room temperature conductivities much higher than the parent unoxidized compound. Studies reveal that for the system $Ni(PC)I_x$, when $x < 1$ I_3^- is present, and when $x > 1$ another species in addition to I_3^- is present. Much further work needs to be done on these systems before they are fully understood. The importance of substituents on the PC ligand is shown by experiments on metal complexes in which the PC ligand contains four electron withdrawing substituents (*e.g.* Cl, NO_2 or SO_2H). No iodine uptake was observed and there was no increase in conductivity.[90]

Two materials of the type $Ni(OMTBP)I_x$ having very different stoichiometries ($x = 1.08 \pm 0.01$ and $x = 2.9 \pm 0.3$) can be isolated following oxidation with I_2. This appears to be the only example of a porphyrinic metallomacrocyclic yielding crystals of different degrees of partial oxidation. The crystal structure of $Ni(OMTBP)I_{1.08}$ consists of a column of the metallomacrocyclic unit with the iodine present as I_3^- in chains parallel to the column.[106] The iodine disorder is severe and the macrocycle is 'puckered' by intramolecular steric hindrance among the exocyclic methyl groups. Because of this non-planarity the Ni(OMTBP) molecules cannot approach one another as closely as the Ni(PC) molecule in Ni(PC)I. However, the crystals exhibit moderately high metal-like conductivities ($\sigma = 10\ \Omega^{-1}\ cm^{-1}$ at 300 K) at and above room temperature.[105]

60.3.2.2 Small ring metallomacrocycles

Iodine oxidation of Ni(OEP) and Cu(OEP) yields polycrystalline materials with a range of stoichiometries.[108] Resonance Raman studies indicate the presence of I_5^- in contrast to the I_3^- observed for larger ring macrocycles. Single crystal studies of Ni(TMP)I indicate a metal-over-metal stack arrangement but with the Ni(TMP) unit puckered. The iodine superlattice is incommensurate with the Bragg lattice.[107] The room temperature conductivity is 10 Ω^{-1} cm^{-1} and increases on lowering the temperature to reach a rounded maximum at 115 K. The spin susceptibility is temperature independent down to a transition temperature of 28 K, well below the conductivity maximum. Below 28 K the susceptibility decreases in an activated fashion with $\Delta/k \approx 60$ K.[108]

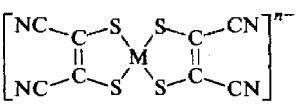
Iodine oxidation of M(TAAB), where M = Pd or Pt, yields compounds of the type [M(TAAB)]$I_{8.1}$. Resonance Raman studies indicate the presence of I_3^- and, therefore, the compound should be formulated as $(MTAAB)^{2.7+}(I_3^-)_{2.7}$. Room temperature conductivities of single crystals are relatively low (Pd, 10^{-7}; Pt, 10^{-4} Ω^{-1} cm^{-1}) but increase by 10^3 (Pd) or 10 (Pt) at 10 kbar pressure.[109]

60.3.2.3 16π-electron tetraazaannulenes

The M(TAA) and M(TMTAA) precursor complexes are known to have highly conjugated planar structures with redox properties similar to the PCs. Iodination yields polycrystalline materials of a wide range of stoichiometries.[90] Resonance Raman studies of $(MTAA)I_x$ and $(MTMTAA)I_x$ show that, for $x < 3$, only I_3^- is present but, for $x \geqslant 3$, I_5^- is also present. The most conducting materials are derived from MTAA complexes, and are comparable to Ni(PC)I. Redox and ESR studies suggest that partial oxidation yields ligand-centred carbon radicals, and single-crystal studies on $Ni(TMTAA)I_{2.44}$ show metal-like behaviour above room temperature.[110]

60.4 METAL DITHIOLENE COMPLEXES

Metal complexes of dithiolene ligands have been extensively studied for the past 20 years.[111,112] The facile redox properties of the complexes in solution suggest that they may be capable of charge transport in the solid state. The terminal substituents can be changed to alter both the electronic and steric properties of the ligand, and thus provide a measure of control of the resulting complex which is absent from purely 'inorganic' ligands such as cyanide or oxalate.



(1) $[M(mnt)_2]^{n-}$

Transition metal complexes (1) of 1,2-dicyanoethylene-1,2-dithiol (maleonitrile), mnt, have received special study since this ligand can stabilize transition metals in a variety of oxidation states and the high electron affinity of the terminal cyanide groups aids the delocalization of charge within the complex, thus reducing potential coulombic repulsions.

60.4.1 Integral Oxidation State Complexes

A wide range of metal dithiolene complexes have been prepared and their electrical conduction properties reported.[111–114] They include neutral, monoanion and dianion complexes with a variety of substituents on the ligand (R = Ph, Me, CN, H, CF_3) and a variety of cations. The choice of cation has often been determined by the desire to obtain easily crystallized products and has resulted in the use of rather bulky substituted ammonium salts. The compounds behave as semiconductors with relatively low conductivities at room temperature. It has been shown that the monoanion complexes are considerably more conducting than either the corresponding neutral complex or the dianion, and Rosseinsky and Malpas have proposed that this is related to the ease of disproportionation.[113]

In 1977, Perez-Albuerne and coworkers reported obtaining relatively higher room temperature conductivities for compressed discs of $Na[M\{S_2C_2(CN)_2\}_2]\cdot 1.15H_2O$ (M = Ni or Pd) ($\sigma \approx 10^{-1}$ Ω^{-1} cm^{-1}) and salts of other small cations.[115] Single crystals of $NH_4[Ni\{S_2C_2(CN)_2\}_2]\cdot H_2O$ were grown by electrocrystallization from an aqueous solution of $(NH_4)_2[Ni\{S_2C_2(CN)_2\}_2]$.[116] Preliminary X-ray studies suggested a uniform stack structure with an Ni—Ni spacing of 3.92 Å.

The conductivity in the stack direction is $5 \times 10^{-2}\ \Omega^{-1}\ cm^{-1}$ and the compound displays semiconductor behaviour from room temperature down to 110 K with a transition between 220–180 K.[116]

The structure of $Rb[Pt\{S_2C_2(CN)_2\}_2]\cdot 2H_2O$ contains the planar anions arranged in a dimeric eclipsed configuration to form a columnar stacked structure.[117] The conductivity in the metal atom chain direction is $2.5 \times 10^{-5}\ \Omega^{-1}\ cm^{-1}$.[117] Polycrystalline samples of compounds of the type $M'[M''(mnt)_2]\cdot x$(solvent), where M′ and M″ are divalent transition metal cations, have been prepared. Conductivities as high as $5 \times 10^{-2}\ \Omega^{-1}\ cm^{-1}$ have been observed for compounds where M′ is Cu^{II} and M″ is Ni^{II}.[118] This work has been extended to salts in which M^{II} is Pt^{II} or Pd^{II}.[119]

The crystal structure and electrical conduction properties of $(Et_4N)_{0.5}[Ni(dmit)_2]$ (where dmit = isotriethione dithiolate) have been reported.[120] In the crystal, face-to-face stacking and side-by-side arrangement of $Ni(dmit)_2$ molecules form a two-dimensional S—S network. The compound is an anisotropic semiconductor with a maximum conductivity of $4.5 \times 10^{-2}\ \Omega^{-1}\ cm^{-1}$ in the stack direction.[120]

60.4.2 Non-integral Oxidation State Compounds

In an attempt to maximize interactions between the metal dithiolene anions, Underhill and Ahmad studied the lithium salt of the $[Pt\{S_2C_2(CN)_2\}_2]$ cation.[121,122] Slow aerial oxidation of a 50% aqueous acetone solution of $H_2[Pt\{S_2C_2(CN)_2\}_2]$ and LiCl yielded a black microcrystalline product of small shining black needles and black platelets. Four-probe DC conduction studies on the needle-shaped crystals showed the room temperature conductivity along the needle axis to be $\sim 100\ \Omega^{-1}\ cm^{-1}$.

The needle-shaped crystals were a cation-deficient compound $Li_{0.82}[Pt\{S_2C_2(CN)_2\}_2]\cdot 2H_2O$ (LiPt(mnt)). X-Ray studies show that the room temperature structure of LiPt(mnt) consists of stacks of nearly eclipsed $[Pt(mnt)_2]$ anions along the *c* axis, with $c = 3.639$ Å (Figure 10).[123] The unit cell is triclinic and the stacks form sheets along *b* separated along *a* by Li^+ and H_2O. There are short sulfur contacts between the chains within the sheets as well as within the chain, suggesting a relatively two-dimensional network.[123] Although the compound is cation deficient, the long Pt—Pt interchain separation shows that the bonding within the chain cannot be of the simple metal orbital overlap type found for the Krogmann salts (Section 60.2). The high conductivity must therefore result from interaction of the whole anion in the chain direction.

The temperature dependence of $\sigma_\parallel$ for freshly prepared crystals slowly increases with decreasing temperature, with $\sigma_\parallel$ passing through a maximum at about 250 K.[122] The conductivity falls to its room temperature value at about 200 K and then falls rapidly with decreasing temperature. Below 100 K the behaviour is that of a semiconductor with activation energy of about 34 meV.

Crystallographic studies have shown a superstructure below $T_c = 215$ K which is preceded by one-dimensional diffuse scattering typical of a Peierls transition.[124] The position of the diffuse line along *c* indicates that the extent of band filling is 0.41 or 0.59. Studies have shown that the thermopower above T_c is approximately constant and positive, implying hole characteristics for the carriers in the metallic region.[125] Further chemical studies have shown that LiPt(mnt) contains approx. 0.3 protons per platinum in the lattice and, therefore, the extent of band filling is 0.59, in agreement with the thermopower results.[126] Below T_c the thermopower reflects the intrinsic properties of the charge-density wave semiconductor. Magnetic susceptibility studies have revealed the Pauli paramagnetism of the conduction electrons above T_c and a sharp drop in χ_p at 220 K corresponding to the metal–semiconductor transition.[127] Optical reflectivity measurements in the metal atom chain direction show a plasma edge characteristic of a metal with a plasma frequency of ~ 6000–$7000\ cm^{-1}$.[125] Assuming a one-dimensional tight binding approximation to model the electronic structure of LiPt(mnt), this leads to a band width of ~0.4 eV, somewhat lower than that derived from the Pauli susceptibility results.[125]

MO calculations based on the neutral $Pt(mnt)_2$ molecule show that, as expected, the overlap integrals along the face-to-face stacking direction are much larger than the interstack overlap integrals.[124] The overlap integral of the d_{z^2} orbital in the platinum chain is one-tenth of those found in the partially oxidized tetracyanoplatinates because of the large intrachain platinum separation in LiPt(mnt). On the other hand, the intrastack overlap integrals of the S atoms are of the same order as those of the d_{z^2} orbitals of the tetracyanoplatinates. The estimated band-gap is about 0.5 eV. Preliminary studies on the nickel analogue of LiPt(mnt) indicates that it displays similar electrical conduction properties.[126]

On the basis of these extensive studies, LiPt(mnt) behaves as a simple quasi-one-dimensional conductor with a mean-field-like metal–semiconductor transition due to the Peierls instability.

The short S—S distances between adjacent stacks produces sufficient coupling between the chains to give rise to the almost mean field like behaviour at the transition.[125]

Studies have been made of the effect of changing the central metal, the cation and the substituent on the ligand, on the conduction properties of this class of compound.[126,128,114] Unfortunately, although LiPt(mnt) can be obtained as small single crystals, the other systems studied have only been obtained as microcrystalline powders. This has meant that no detailed correlations can be made of structure/chemical composition on the conductivities of these compounds. Attempts to produce analogues of LiPt(mnt) with ligands in which the terminal cyano group was replaced by phenyl, methyl or hydrogen were not successful and only integral oxidation state complexes could be obtained.[114] The electron distribution in the monoanion HOMO is very dependent on the nature of the substituent. Electron withdrawing groups, such as CN, increase the electron density on the metal and reduce it on the S compared with the phenyl substituted ligand. This may aid the intermolecular overlap necessary for the formation of a 1D metal.

The black plates which are formed along with LiPt(mnt) in the acid oxidation of $H_2[Pt\{S_2C_2(CN)_2\}_2]$/LiCl mixtures in acetone–water have been shown to be $Li_{0.5}[Pt\{S_2C_2(CN)_2\}_2]\cdot 2H_2O$.[129] X-Ray studies reveal that the $[Pt(mnt)_2]^{0.5-}$ anions are stacked face-to-face along the *a* axis of the unit cell to form a fourfold distorted linear chain. This can be regarded as the Peierls distorted state analogous to that found in $Rb_{1.67}[Pt(C_2O_4)_2]\cdot H_2O$. The room temperature conductivity ($\sigma_{\|}$) is $\sim 1\ \Omega^{-1}\ cm^{-1}$ and the temperature dependence is that of a semiconductor.[129]

A highly conducting complex, $(NBu_4)_{0.29}[Ni(dmit)_2]$, has been prepared by electrocrystallization. The conductivity in the stacking direction is $10\ \Omega^{-1}\ cm^{-1}$ at 300 K but the temperature dependence indicates a thermally-activated conduction mechanism.[130] A conducting iron complex has also been reported. Compounds of the type $Z_x[Ni(dimt)_2]$, where $x \ll 1$ and Z = Li, Na, Bu_4N, Ph_4P or Ph_3B_2P, have also been prepared following the electrolytic reduction of CS_2. Conductivities as high as $10\ \Omega^{-1}\ cm^{-1}$ have been reported.[132]

Compounds of $[M(dmit)_2]$ anions have also been formed with π-donors such as TTF and TMTTF.[131] $TTF[Ni(dmit)_2]_2$ exhibits a metal-like conductivity temperature dependence down to 4 K with the conductivity increasing from $300\ \Omega^{-1}\ cm^{-1}$ at 300 K to $10^5\ \Omega^{-1}\ cm^{-1}$ at 4 K.[131]

A recent paper presents a very comprehensive account of the dimerization and stacking in transition metal bisdithiolenes and tetrathiolates based on MO and band structure calculations.[162]

60.5 MIXED VALENCE COMPLEXES

These compounds belong to the Robin and Day's Class II systems in which the metal atoms exist in two distinct and integral oxidation states.[4] A wide variety of examples of this type of compound were discussed at a NATO ASI.[133]

60.5.1 Linear-chain Halogen-bridged Mixed Valence Complexes

These are one of the most studied classes of mixed valence complexes and have been reviewed recently by Keller and by Clark.[134,135] They all possess a common structural unit $X\cdots M^{II}\cdots X\cdots M^{IV}\cdots X\cdots M^{II}\cdots X$. Table 5 gives a selection of examples for which electrical conduction studies are available with particular emphasis on results obtained on single crystals. The compounds are arranged depending on the charge of the complex.

Single crystals of these complexes exhibit room temperature conductivities in the chain direction ranging from 10^{-15} to $10^{-8}\ \Omega^{-1}\ cm^{-1}$. The crystals behave as semiconductors with a well defined activation energy. It can be seen that the conductivity is unaffected by the charge on the complex and is also little affected by changing the neutral ligands. For all these types of complexes the conductivity increases and the activation energy decreases in the order X = Cl < Br < I and M = Pt < Pd < Ni. In this order η (where η = M^{IV}—X bond length/M^{II}—X bond length) becomes larger and closer to unity.

The parameter η measures the crystallographic difference between the M^{II} and M^{IV} sites. PES studies show that the electronic difference also becomes less as η increases.[144] If X came to the midpoint between M^{II} and M^{III} (*i.e.* $\eta = 1$) then all the M ions would become equivalent and a similar situation to the Krogmann salts might be expected, with very high conductivities. The position of the intervalence band is also strongly dependent on η and moves to lower frequencies as η approaches unity.[145]

Table 5 Halogen-bridged Mixed Valence Compounds

Compound	σ (Ω^{-1} cm^{-1})	ΔE (meV)	η	*Ref.*
Cationic complexes				
$[Ni(en)_2][Ni(en)_2Cl_2](ClO)_4$	1.3×10^{-8}	570	—	136
$Ni(pn)_2Cl_3$	1.3×10^{-7}	350	—	137
$Ni(cyn)_2Cl_3$	2.6×10^{-7}	240	—	137
$[Pd(tt)][Pd(tt)Cl_2](ClO_4)_4$	10^{-10} P	—	0.72	138
$[Pd(en)_2][Pd(en)_2Cl_2](ClO_4)_4$	2.0×10^{-12} P	810	0.77	136
$[Pd(en)_2][Pd(en)_2Br_2](ClO_4)_4$	1.2×10^{-8} P	490	0.96	136
$[Pt(en)_2][Pt(en)_2I_2](ClO_4)_4$	1.8×10^{-8}	420	0.92	136
$[Pt(tn)_2][Pt(tn)_2Br_2](ClO_4)_4$	2.0×10^{-14}	1210	0.86	139
$[Pt(tn)_2][Pt(tn)_2I_2](ClO_4)_4$	7.0×10^{-7}	370	—	139
$[Pt(en)_2][Pt(en)_2I_2](BF_4)_4$	1.6×10^{-9}	460	—	139
$[Pt(en)_2][Pt(en)_2Cl_2](ClO_4)_4$	2.0×10^{-15}	1350	0.75	136
$[Pt(en)_2][Pt(en)_2Br_2](ClO_4)_4$	3.0×10^{-11}	840	0.86	136
Neutral complexes				
$[Pd(NH_3)_2Cl_2][Pd(NH_3)_2Cl_4]$	2×10^{-9}	350	0.62	140
	4×10^{-9}	350		141
$[Pd(NH_3)_2Br_2][Pd(NH_3)_2Br_4]$	5×10^{-8} P	300P	—	140
$[Pd(NH_3)_2Cl_2][Pt(NH_3)_2Cl_4]$	3×10^{-11} P	—	0.62	141
$[Pt(NH_3)_2Br_2][Pt(NH_3)_4Br_2]$	3×10^{-9}	520	0.64	140
$[Pt(en)Cl_2][Pt(en)Cl_4]$	1×10^{-15}	1700	—	140
$[Pt(en)Br_2][Pt(en)Br_4]$	5×10^{-13}	1200	—	140
$[Pt(en)I_2][Pt(en)I_4]$	1×10^{-9}	690	—	140
$Cs_2[Pt(NO_2)(NH_3)Br_2][Pt(NO_2)(NH_3)Br_4]$	8×10^{-13}	720	0.75	142
$Cs_2[Pt(NO_2)(NH_3)I_2][Pt(NO_2)(NH_3)I_4]$	3×10^{-9}	630	0.81	142
$K_4[PtI_4][PtI_6]$	1×10^{-8}	600	0.85	143

P compressed pellet; pn = 1,2-diaminopropane; cyn = 1,2-diaminocyclohexane; tt = 1,4,8,11-tetraazacyclotetradecane.

The conductivities of this type of compound increase dramatically with increasing pressure. Studies of the $[M(en)_2][M(en)_2X_2]ClO_4$ complexes showed that the conductivity increased by a factor of 10^3 under 7 kbar pressure but that the activation energy was less affected.[136] Pressures of 140 kbar on the neutral chain $M(NH_3)_2X_3$ complexes produced an increase in conductivity of about six orders of magnitude and a reduction in the M^{II}—M^{IV} separation of over 0.2 Å at 60 kbar.[140]

The electrical conductivity of these compounds has been found to be strongly frequency dependent and this has been interpreted as indicating a conduction mechanism involving hopping of carriers between essentially localized states. ESR measurements indicate that the carrier activation centre is about one per 10^4 Pt sites and may be located at structural dislocations or thermal defects in the chain.[136] The optical mode oscillation frequency $h\nu$ in the M—X—M chain has been calculated from resonance Raman and IR data.[146] The values obtained are similar to the activation energy for carrier generation deduced from ESR studies. This activation energy is smaller by 10 or 10^2 than the conduction activation energy ΔE, and therefore the dominant part of ΔE is not carrier generation but the successive transport process among localized states in the d_{z^2} band. A strong correlation between $\log \sigma_0 \propto \Delta E$ exists for many different compounds of this type, since the transport mobility, μ, due to the tunnelling process should be strongly dependent on the barrier height above the activation energy ΔE.

Studies have also been made on mixed valence gold compounds of the type $Cs_2[AuI_2][AuI_2][AuI_4]$, $\sigma = 5 \times 10^{-1}$ Ω^{-1} cm^{-1} (P), and $Cs_4M^{II}[AuCl_6]_2$ where M = Cu, Pd, Zn, Cd or Hg.[21] Recently an unusual compound containing dimeric $Pt_2(MeCS_2)_4$ units linked by halogen bridges has been reported.[147] The conductivity for a compressed disc of the iodo complex is 7×10^{-3} Ω^{-1} cm^{-1}, reflecting an η value very close to unity (0.99). The activation energy is 50 meV.

60.6 MISCELLANEOUS COMPOUNDS

60.6.1 Magnus' Green Salt

Magnus' Green Salt (MGS) contains chains of alternating $[Pt(NH_3)_4]^{2+}$ cations and $[PtCl_4]^{2-}$ anions with a Pt—Pt separation of 3.245 Å. Early reports of high electrical conductivities have

been shown to be due to high levels of Pt^{IV} impurities and have also shown that MGS is an extrinsic semiconductor.[148,149]

Treatment of MGS with 62% sulfuric acid and O_2 gas at room temperature for several weeks converts the green salt to a brown powder with a metallic lustre. The product $Pt_6(NH_3)_{10}Cl_{10}(HSO_4)_4$ is a partially oxidized salt (MGSPOS).[150] The crystal structure of this compound has not been determined but X-ray studies show that the intrachain Pt—Pt distance (3.25 Å) is the same as in MGS and much longer than that found in the Krogmann salts. Compared with MGS it is proposed that some of the Cl^- and NH_3 ligands have been replaced by HSO_4^- and that the size of these ligands prevents any decrease in the Pt—Pt separation. The average oxidation state of the Pt is 2.33 but XPS studies show that the compound is a mixed valence system. The DC conductivity is $10^{-4}\ \Omega^{-1}\ cm^{-1}$ for compressed pellets at room temperature, and the temperature dependence of the conductivity is complex with a maximum at 240 K.[150] Copper coloured needles obtained by the reaction of MGS in $HClO_4$ with chloro(hydroxo)Pt^{IV} complexes contain two types of platinum atom chains. One chain contains fully interacting Pt atoms only 2.85 Å apart whilst the other is of the mixed valence bridged type. The room temperature conductivity is $10^{-1}\ \Omega^{-1}\ cm^{-1}$ (pressed disc) with an activation energy of 50 meV.[151] Galvostatic oxidation of MGS in H_2SO_4 also produces MGSPOS with conductivities as high as $10^{-1}\ \Omega^{-1}\ cm^{-1}$ for some samples and with a conductivity maximum at 190 K.[152]

60.6.2 Metal Isocyanide Complexes

Several different types of metal isocyanide complex exhibit solid state optical properties indicative of metal–metal interactions, but most exhibit low electrical conductivities.[21] One series of salts $[Rh(CNR)_4]X^-$, where R = phenyl, vinyl, ethyl or methyl and X = Cl, PF_6, BF_4 or ClO_4, exhibit much higher conductivities and Rh—Rh separations as short as 2.94 Å.[153] Single crystals of $[Rh(CNCHCH_2)_4]ClO_4$ have a room temperature conductivity of $2\ \Omega^{-1}\ cm^{-1}$ with an activation energy of 100 meV. An indication of a metallic state was observed below the decomposition temperature of 330 K but it was not possible to conclude whether the high conductivity was the result of partial oxidation, small band gap intrinsic semiconductor behaviour or extrinsic semiconductor behaviour due to Rh^{II} 'impurities'. More recent studies indicate the existence of polynuclear species but a full structural study of an infinite metal atom chain compound with isocyanide ligands has not been made.[154]

60.6.3 Coordination Polymers

Doping of the cofacially linked oligomers $[M(Pc)O]_n$ (M = Si, Ge, Sn; Pc = phthalocyaninato) with halogen (I_2, Br_2) or quinone electron acceptors produces robust electrically conductive polymers with conductivities as high as $1\ \Omega^{-1}\ cm^{-1}$.[155–157] Polymeric phthalocyaninatometal complexes (M = Fe, Ru or Co) with pyrazine, tetrazine or 1,4-diisocyanobenzene have been shown to exhibit conductivities as high as $10^{-2}\ \Omega^{-1}\ cm^{-1}$ without doping.[158] Conducting polymers can also be produced by using polydentate sulfur donor ligands capable of chelating to two metal atoms, and conductivities of up to $1\ \Omega^{-1}\ cm^{-1}$ have been achieved.[119,159]

60.6.4 Halotricarbonyliridium Complexes [$Ir(CO)_3X$; X = Cl, Br or I][85]

In 1968, Krogmann and coworkers characterized what they concluded to be a partially oxidized material, $Ir(CO)_{2.93}Cl_{1.07}$, from the action of CO on $IrCl_3 \cdot H_2O$ and containing iridium atom chains with short intrachain separation. Later studies indicated conductivities of $0.2\ \Omega^{-1}\ cm^{-1}$ for single crystal samples. Detailed studies of the compound including optical, Mössbauer, X-ray structure and mass spectra studies have concluded that the compound is stoichiometric and should be formulated as $Ir(CO)_3Cl$.[160] The 'metallic' properties of high conductivity and short intrachain Ir separation (2.844 Å) are indicative of a semimetal arising from possible overlapping of $5d_z$–$6p_z$ bands. SCF–Xα–SW calculations suggest extensive mixing of metal and ligand band orbitals.[85]

$Ir(CO)_3Br$ is isostructural with the chloro complex but with a slightly longer intrachain separation (2.854 Å). The four-probe DC conductivity in the iridium atom chain direction is, however, only $3 \times 10^{-4}\ \Omega^{-1}\ cm^{-1}$ and this, together with the variation of conductivity and thermopower with temperature, indicates that the bromo complex is a semiconductor.[161] The structure of $Ir(CO)_3I$ shows more disorder and could not be refined accurately, but the Ir—Ir separation is 2.858 Å.

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61.1

Stoichiometric Reactions of Coordinated Ligands

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61.1.1 INTRODUCTION

The synthetic utility of reactions of coordinated ligands is an important and varied subject. It is based on the enhancement in reactivity of organic ligands as a consequence of metal coordination. For example, the metal can act as a 'super acid' and cause enhanced nucleophilic attack on coordinated carbonyl and imine ligands. The metal ion can also enable the ligand itself to act as a nucleophile, sometimes by direct activation, sometimes by protecting other parts of the ligand and sometimes by a combination of both.

The ligands which undergo reaction can be bound to the metal ion in the transition state or in relatively stable, isolable complexes. There is often a geometrical or stereochemical factor in ligand reactions and this factor is manifest in the so-called template reactions.

Chapter 7.4 contains a discussion of the types of ligand reactions, based on their likely mechanisms, and includes an account of the various template effects. A brief summary of such mechanistic aspects is relevant here as a backdrop for a more detailed account of stoichiometric ligand reactions of synthetic utility. Some ligand reactions take place in complexes in which there is no dissociation of the ligand from the metal. In extreme cases, the metal can be irrelevant, or can be entirely responsible for activation, but usually the situation is somewhere in between the two. Many examples exist in which the metal ion acts as a 'super acid' and causes reactions to occur at enhanced rates. Reaction can occur either at the donor atom or at a more remote position from the metal. New chelate rings can be formed when reaction occurs between two ligands attached to the same metal ion. Such reactions are enhanced by kinetic template effects arising from the intramolecular nature of the process. Electronic activation can still be important in these reactions, but in most cases the geometrical feature is paramount. Sometimes, metal coordination is a transient feature of ligand reactions, causing a lowering of the transition state energy and promoting the reaction. A metal ion can also effect changes in equilibria and stabilize tautomers which form stable chelate rings. The thermodynamic or equilibrium template effect can thus allow the isolation of complexes containing ligands which can not be isolated in their un-coordinated state from normal organic reactions. Other thermodynamic template reactions might not necessarily produce unique ligands, but can be used as an effective synthetic tool because of the promotion of reaction and the ease of isolation of the metal complex product.

Consideration of synthetic utility of reactions of coordinated ligands must therefore take into account the synthesis of ligands promoted by metal coordination, in addition to direct reactions of metal complexes.

The main use of ligand reactions in synthesis is in the construction of multidentate chelates. In this manner, the field of coordination chemistry has been enriched, as the development of new ligands has led to the introduction of new influences in metal ions. The various properties of coordination compounds are considered elsewhere in this book, but this chapter will focus attention on the synthesis of new ligands and complexes as a consequence of ligand reactions.

In an increasingly impressive number of examples, some ligands which are built up around metal ions can be freed subsequently from their controlling metals to provide a new aspect to organic synthesis. Such a synthetic strategy enables the formation of polyfunctional compounds and is increasingly being used for its stereochemical ability to offer stereoselectivity.

In contrast to Chapter 7.4, which is organized according to reaction type, this chapter will consider a selection of topics in order to give a clearer and broader perspective of synthetic utility. Template syntheses of metal complexes and the subsequent reactions of their ligands will be considered together, so that an overall picture of a particular area of research can be presented more cohesively. Emphasis will be on major areas of research and no attempt will be made to present an exhaustive coverage.

The first section will consist of the synthesis and reactions of imine chelates, as this is the most widely and consistently used aspect of ligand reactions. The discussion will be subdivided according to the types of ligands involved and will range from bidentate through to multidentate ligands, macrocycles and cage compounds.

A consideration of the synthesis and reactions of phthalocyanines, porphinoids, corrinoids and related macrocycles will follow in the second section. Discussion in this section will be restricted because these topics will receive consideration in other chapters.

The third section will contain direct reactions of stable chelates. This is a large and diffuse topic and many examples of reactions of this type are included in Chapter 7.4. In the current chapter, a more detailed discussion of the most important areas, namely complexes of β-diketones and α-amino acids and their derivatives, will be offered. Also some important organic reactions of carbonyl compounds will be considered with regard to the nature of their chelated transition states and the effects these have on product formation.

Various aspects of this subject have been reviewed, but most reviews are not recent and none consider the topic from the present point of view. However, the reader is referred to reviews by Busch,[1] Dwyer,[2] Black and Markham,[3] Collman,[4] Lindoy,[5,6] Black and Hartshorn,[7] Healy and Rest[8] and Melson.[9]

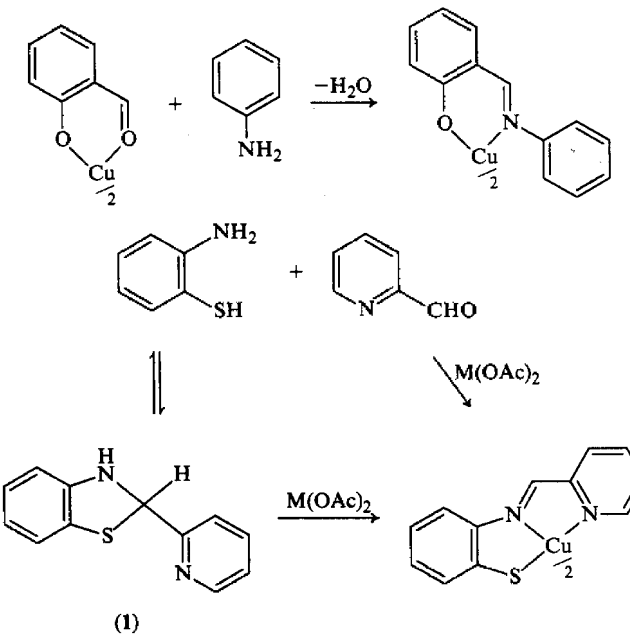
61.1.2 SYNTHESIS AND REACTIONS OF IMINE CHELATES

61.1.2.1 Simple Imines Formed by Thermodynamic Template Reactions

The formation of imine or Schiff base metal complexes can be effected very readily by arranging for reaction of the amine with the carbonyl compound to take place in the presence of the metal ion. Nucleophilic attack of the amine on the carbonyl group is enhanced by polarization of the carbonyl group by coordination of the oxygen atom to the metal ion. Furthermore, the reaction is reversible unless steps are taken to effect dehydration of the intermediate hydroxy amine, and coordination of the product imine is an important factor in the promotion of the reaction by suitable metal ions.

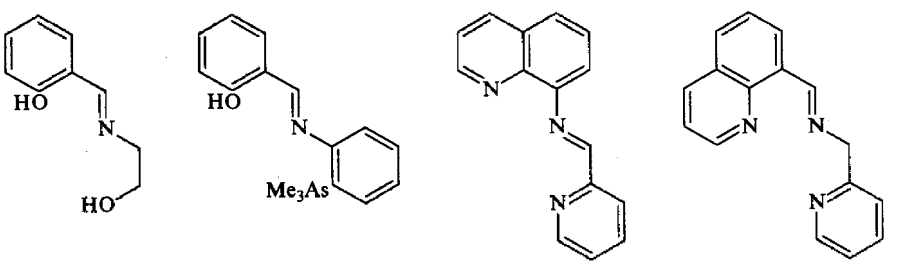
The initial reactions of this type were used to produce copper(II) complexes of salicylaldimines, where additional coordination support is provided by the phenolic oxygen atoms (equation 1).[10,11] Similar use can be made of pyridine-2-carbaldehyde in the formation of imine chelates. For example, the combination of pyridine-2-carbaldehyde and 2-aminobenzenethiol in the presence of metal ions yields tridentate complexes (Scheme 1).[12] If the reaction is carried out in the absence of the metal ion, the benzothiazolidine (**1**) is isolated. Thus the metal ion is essential for the formation of the imine product in this case. Metal complexes of the related tridentate ligands (**2**),[13] (**3**),[14] (**4**)[15] and (**5**)[16] can be prepared similarly.

The synthesis of quadridentate imine chelates usually requires the combination of two equivalents of the carbonyl compound and a diamine, as in the formation of complexes of ligands (**6**),[17,18] (**7**)[19] and (**8**).[20,21] In similar fashion, thermodynamic template reactions allow the very effective synthesis of quinquedentate and sexadentate metal complexes of ligands such as (**9**),[22] (**10**),[23] (**11**),[24] (**12**)[25] and (**13**).[26] Condensation of 1,1,1-tris(aminomethyl)ethane with pyridine-2-carbaldehyde alone yields

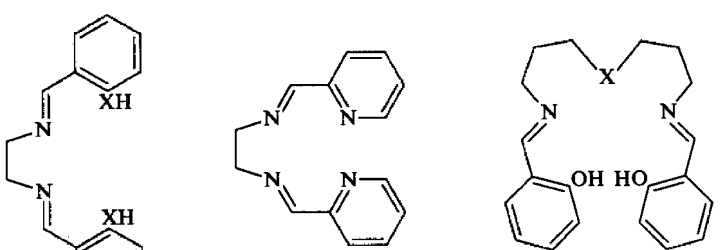


(1)

Scheme 1



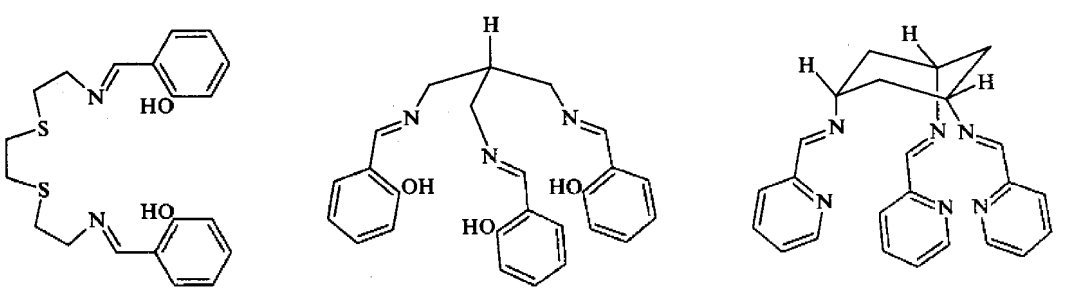
(2) (3) (4) (5)



(6) X = O
(7) X = S

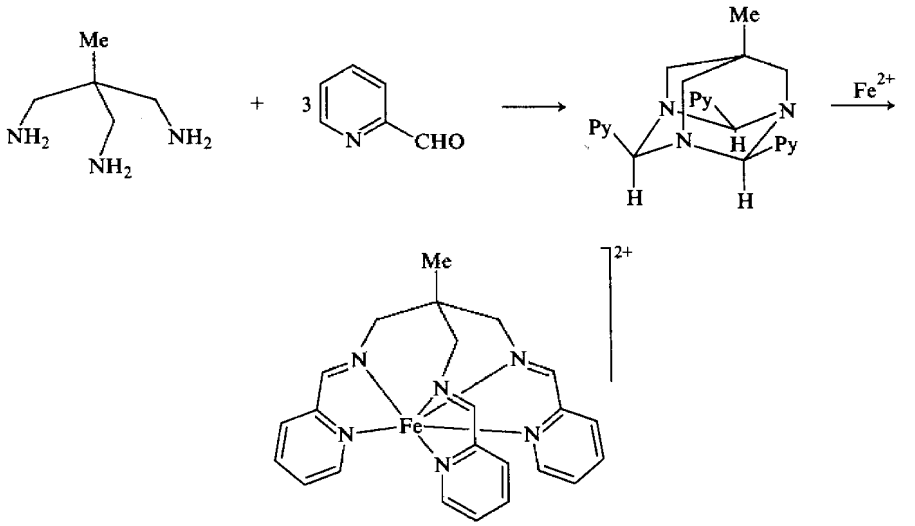
(8)

(9) X = NMe
(10) X = S



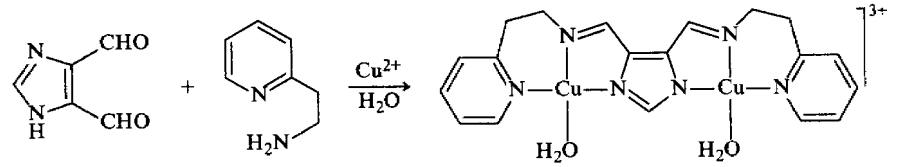
(11) (12) (13)

a cyclic product which undergoes reaction with iron(II) salts to give a sexadentate tris-imine complex (Scheme 2).[27,28]

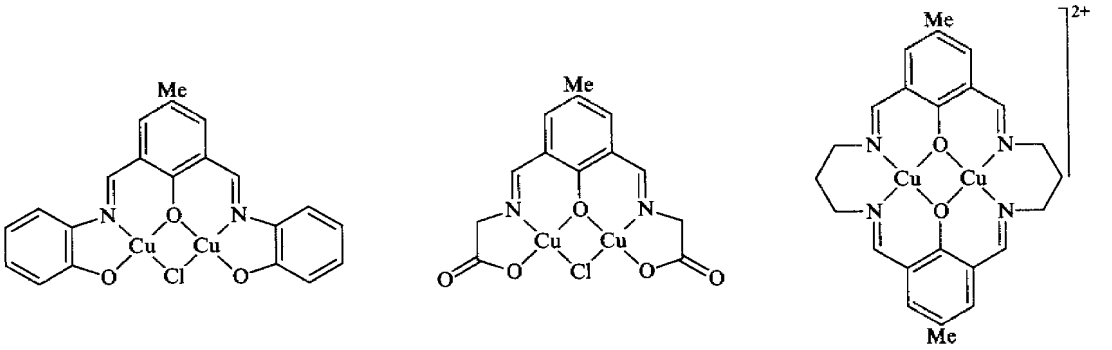


Scheme 2

The reaction of imidazole-4,5-dicarbaldehyde with 2-aminoethylpyridine in the presence of copper(II) chloride has enabled the preparation of a binuclear complex (equation 2).[29] A more common class of binuclear complex is based on template reactions of a phenolic dialdehyde with various amines and includes the copper complexes (**14**)[30,31] and (**15**).[32] Reactions of this type can be extended to the synthesis of macrocyclic binuclear complexes such as (**16**).[33,34]

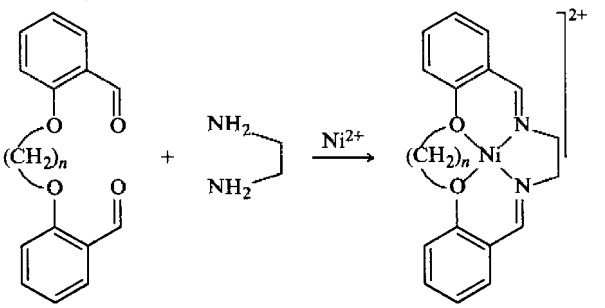


(2)

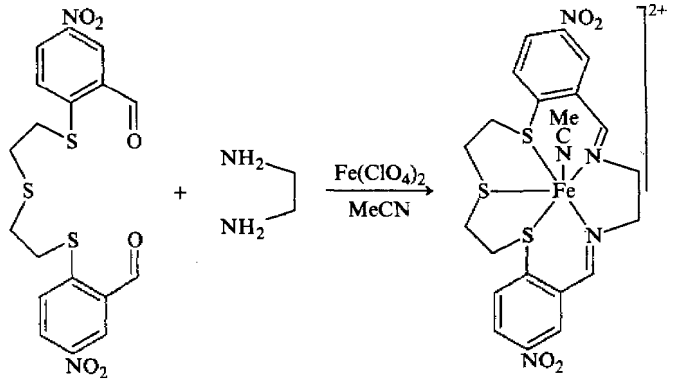


(**14**) (**15**) (**16**)

Simple macrocyclic quadridentate complexes can be synthesized by template reactions from ethers derived from salicylaldehyde and diamines in the presence of appropriate metal ions such as nickel(II) (equation 3).[35,36] However, these reactions can also be carried out quite effectively in the absence of metal ions to yield the free ligands, which can be obtained by hydrolysis of the complexes. An iron(II) macrocyclic quinquedentate chelate of this type has been produced by template synthesis (equation 4).[37]

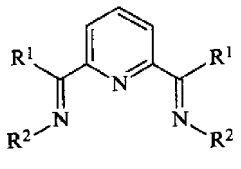


(3)

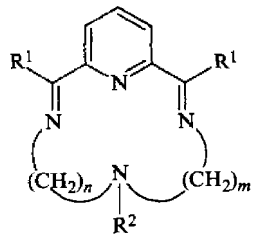


(4)

Pyridine-2,6-dicarbaldehyde and 2,6-diacetylpyridine have been widely used in the template synthesis of imine chelates ranging in complexity from linear tridentates, such as (**17**),[38,39] to macrocyclic structures with a range of ring sizes, such as (**18**).[40–42] The *in situ* formation of macrocyclic ligands of this type depends upon the ring size and the strength of complexation of the triamine by the metal ion at the pH of the reaction. Related complexes with an additional donor atom attached to R^2 have been synthesized also.[43,44]

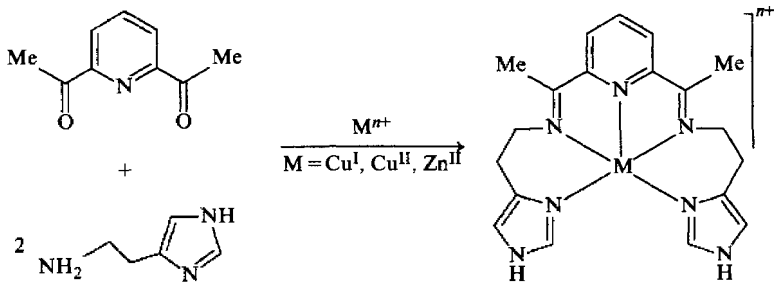


(**17**) R^1 = H, Me
R^2 = alkyl, aryl

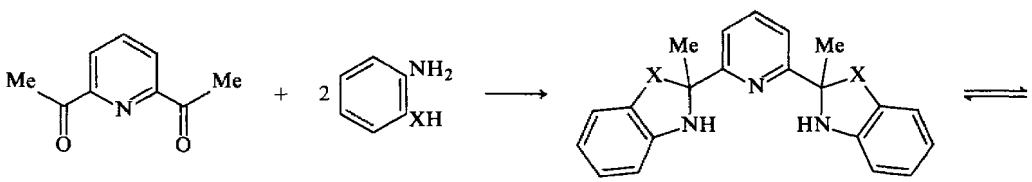


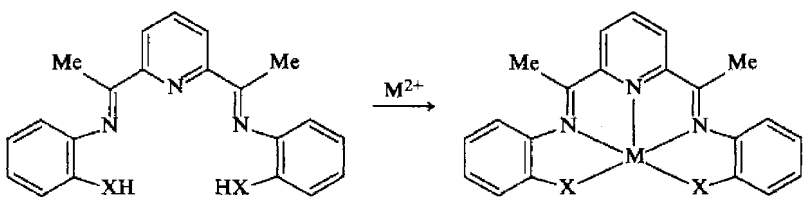
(**18**) R^1 = H, Me
R^2 = H, alkyl
n = 2, 3; m = 3, 4

Before completing the discussion of linear chelate systems related to compounds (**17**), it is noteworthy that a range of quinquedentate chelates can be obtained by means of condensation of the dialdehyde with 4-aminoethylimidazole (equation 5)[45] and 2-aminobenzenethiol (Scheme 3).[46,47] In the latter case, the metal exerts an effect on the equilibrium between the cyclic and diimine structures.



(5)

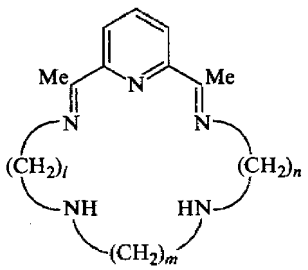




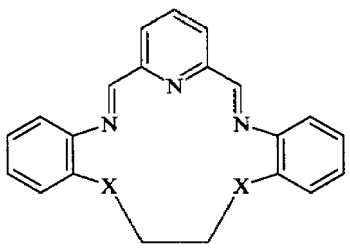
X = O, S; M = Zn, Cd

Scheme 3

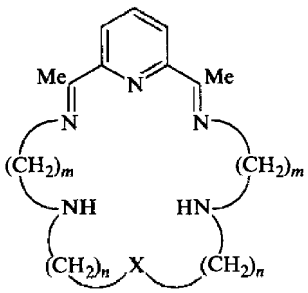
Further macrocyclic structures containing five or six donor atoms can be produced by means of various different templating metals. For instance, complexes of ligands (**19**), (**20**) and (**21**) can be synthesized for silver(I), magnesium(II), zinc(II), cadmium(II), mercury(II) or manganese(II).[48–50] Phosphorus donor atoms have been introduced in the form of a nickel(II) complex of ligand (**22**)[51] and silver(I) and cadmium(II) complexes of ligands (**23**).[52] Lead(II) has been found to be a most successful templating metal for macrocycles containing oxygen as well as nitrogen donor atoms.[53,54] This technique has also been used to synthesize larger macrocyclic ligands such as (**24**) and (**25**).[54,55] Both ligands allow the preparation of binuclear copper(II) complexes and a dilead complex of ligand (**25**) has been formed by a direct template reaction. Similar macrocycles based on furan-2,5-dicarbaldehyde have been prepared using a barium(II) template and a binuclear copper(II) complex of ligand (**26**) has been obtained.[56,57]



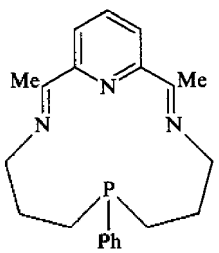
(**19**) *l*, *m*, *n* = 2, 3



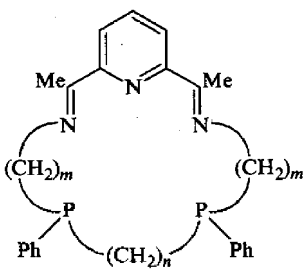
(**20**) X = O, NH



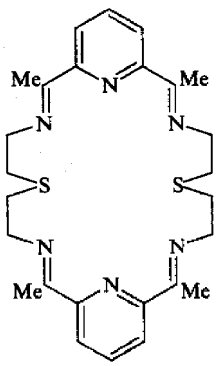
(**21**) X = O, NH; *m*, *n* = 2, 3



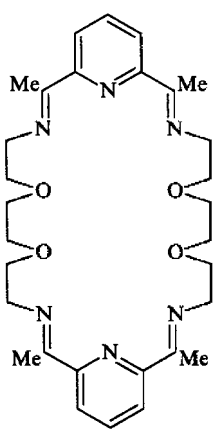
(**22**)



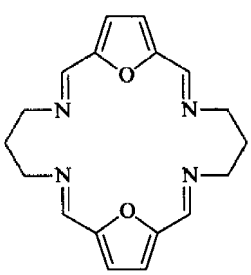
(**23**) *m*, *n* = 2, 3



(**24**)



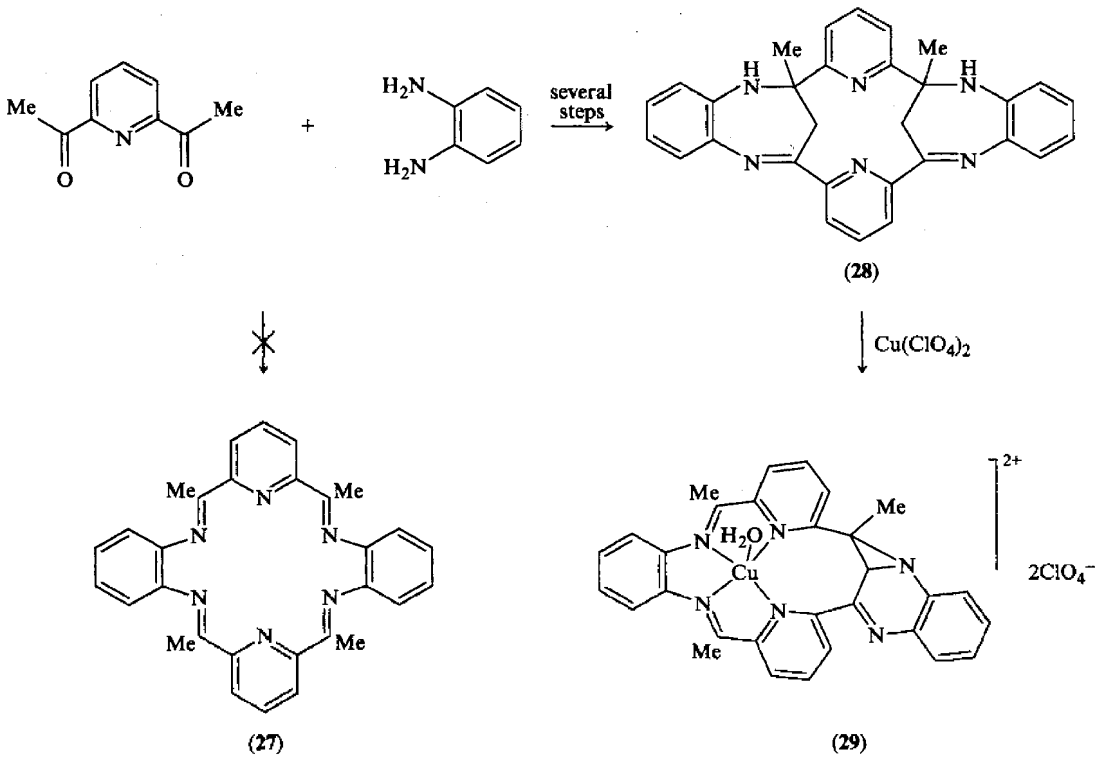
(**25**)



(**26**)

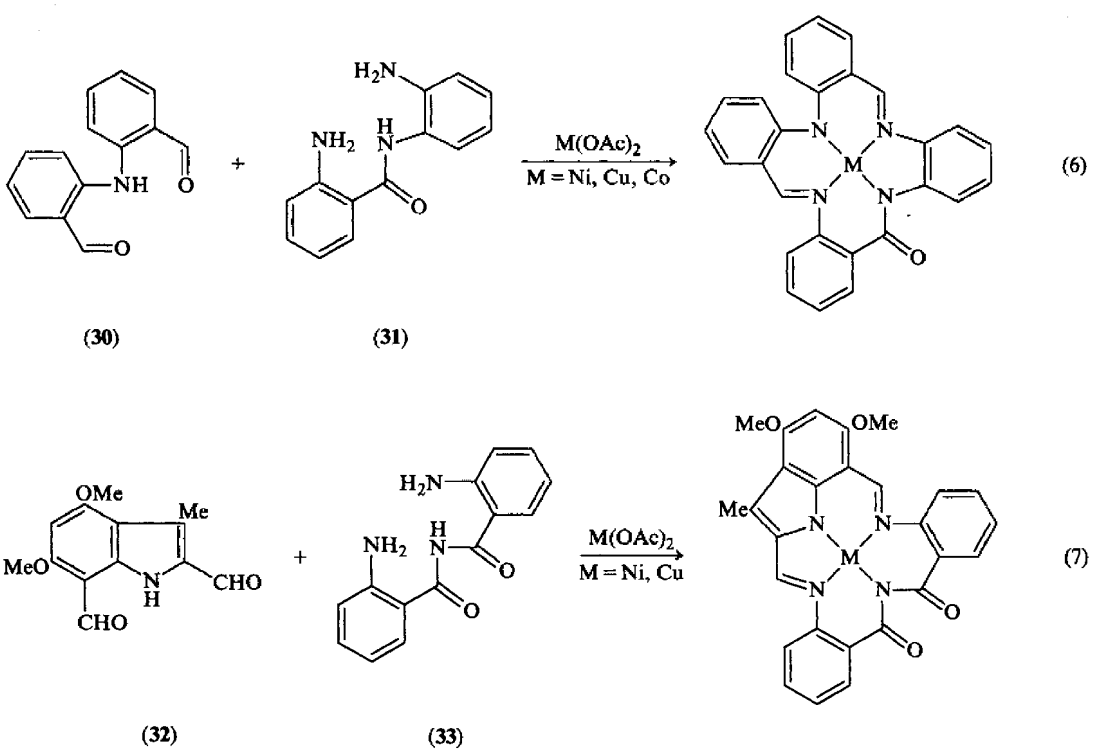
In a recent development, the ligand previously claimed to be the simple tetraimine macrocycle (**27**) has been shown by X-ray crystallography to have the polycyclic structure (**28**).[58] This compound undergoes the rather extraordinary template rearrangement promoted by copper(II) perchlorate to yield the diimine complex (**29**) (Scheme 4).[59]

Template reactions of dicarbonyl compounds and diamines have been extended recently to include the dialdehydes (**30**)[60,61] and (**32**)[62,63] and a range of new diamines such as (**31**) and (**33**).[64] Examples are shown in equations (6) and (7). The new diamines have also been used in the template synthesis of macrocyclic complexes based on 2,6-diacetylpyridine.[60,65]



(27) (28) (29)

Scheme 4



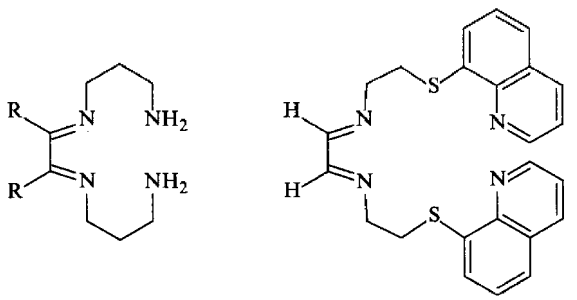
(30) (31) (6)

(32) (33) (7)

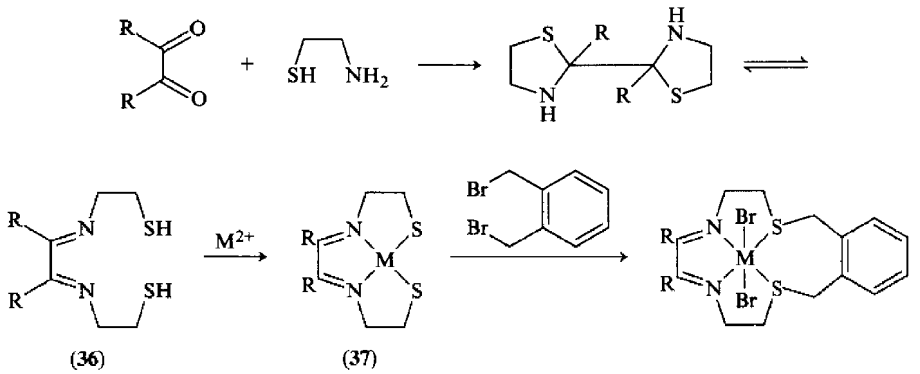
The reactions of simple imine complexes are mainly restricted to hydrogenation or reduction by hydrides or by addition of nucleophiles such as alcohols. For example, complexes of macrocycles (**18**) undergo catalytic reduction to generate two chiral centres.[66] Sodium borohydride has been used to reduce the imine complexes shown in equation (3).[67] This technique enables convenient removal of the metal and the consequent synthesis of the reduced free macrocycles. Complexes of the aldimine (**20**) undergo nucleophilic addition of alcohols.[49]

61.1.2.2 α-Diimines

Simple α-diimines are hydrolytically unstable, but can be stabilized as metal complexes by virtue of the formation of stable five-membered chelate rings.[68,69] α-Diketones and glyoxal undergo metal template reactions with amines to yield complexes of multidentate ligands such as (**34**),[70] (**35**)[71] and (**36**).[72,73] In the last case, the metal exerts its stabilizing influence on the α-diimine partner in an equilibrium process (Scheme 5). The same phenomenon occurs with amino alcohols[74,75] in addition to amino thiols. The thiolate complexes (**37**) can be converted to macrocyclic complexes by alkylation in a kinetic template reaction (Scheme 5).[76,77]



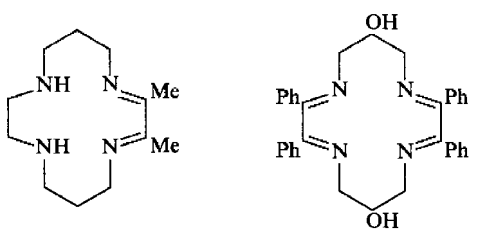
(**34**) (**35**)



(**36**) (**37**)

Scheme 5

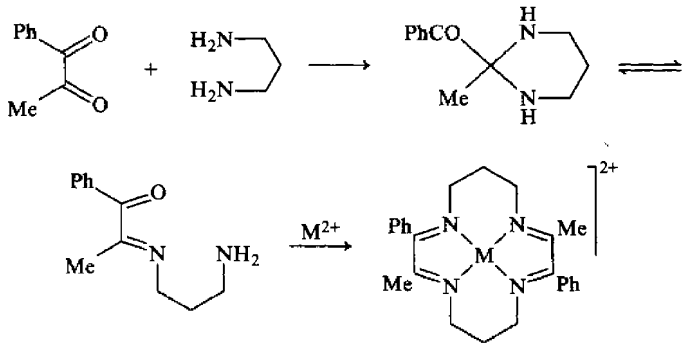
Template reactions between α-diketones and diamines have been used for the synthesis of complexes of macrocyclic ligands such as (**38**)[78] and (**39**).[79] Some insight into the mechanism of the formation of these macrocycles has been provided by some recent work which shows the value of the thermodynamic template effect (Scheme 6).[80]



(**38**) (**39**)

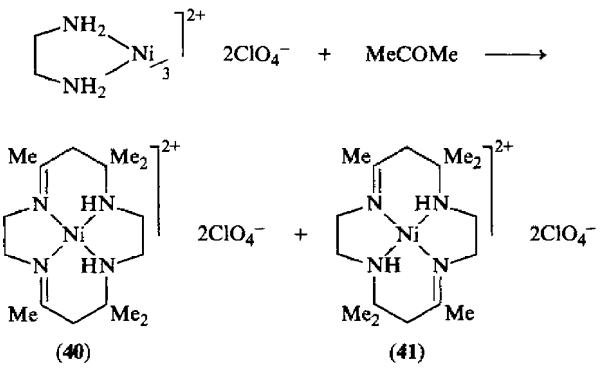
61.1.2.3 β-Amino Imines

Metal template syntheses of complexes incorporating the β-amino imine fragment have been introduced by Curtis as a result of his discovery that tris(1,2-diaminoethane)nickel(II) perchlorate reacted slowly with acetone to yield the macrocyclic complexes (**40**) and (**41**) (equation 8).[81–83] In this macrocyclic structure the bridging group is diacetone amine imine, arising from the aldol condensation of two acetone molecules. This reaction is widely general, in the same way that the aldol reaction is, and can be applied to many types of amine complexes. The subject has been reviewed in detail with respect to macrocyclic complexes by Curtis.[84]



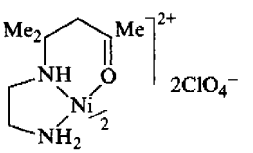
Scheme 6

Reaction of bis(1,2-diaminoethane)nickel(II) perchlorate with acetone allows the isolation of the β-amino ketone complex (**42**), which can be converted in pyridine to the *trans* macrocyclic complex (**41**). A similar reaction occurs with methyl ethyl ketone (Scheme 7).[85]

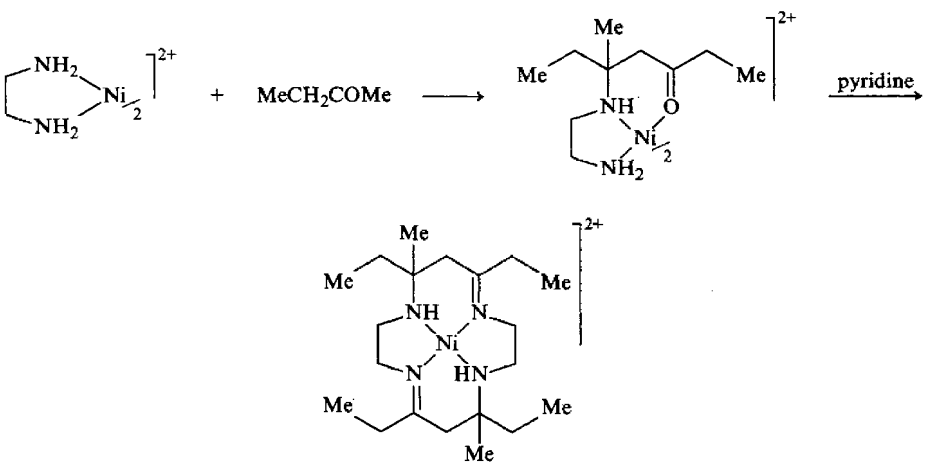


(8)

(**40**) (**41**)



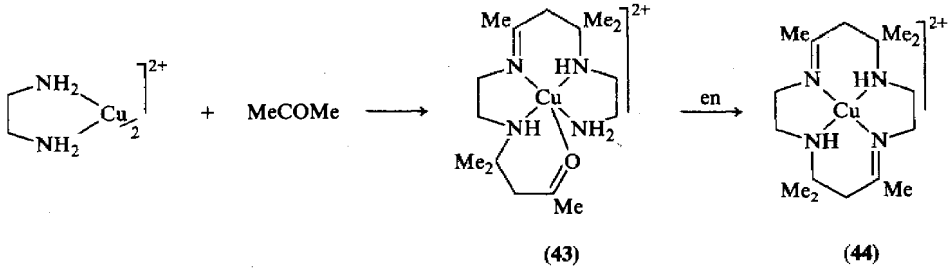
(**42**)



Scheme 7

Bis(1,2-diaminoethane)copper(II) perchlorate undergoes reaction with acetone to give the quinquedentate complex (**43**), which is converted to the macrocyclic complex (**44**) on addition of base, usually excess 1,2-diaminoethane (Scheme 8).[86] Similar cobalt(II) complexes cannot be prepared by metal template methods.

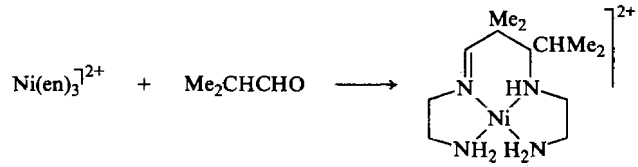
The generality of the template reaction can be extended to more hindered carbonyl compounds, but the reactions become very much slower. 2-Methylpropanaldehyde undergoes reaction with



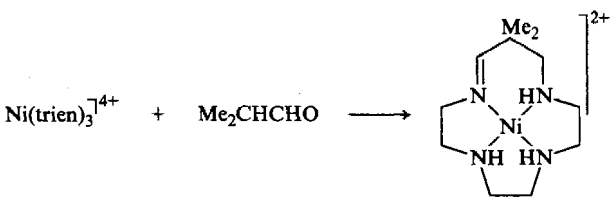
(43) (44)

Scheme 8

1,2-diaminoethane complex to give the expected non-macrocyclic complex (equation 9), but yields an unexpected product in reaction with a complex of 1,8-diamino-3,6-diazaoctane (equation 10).[87]

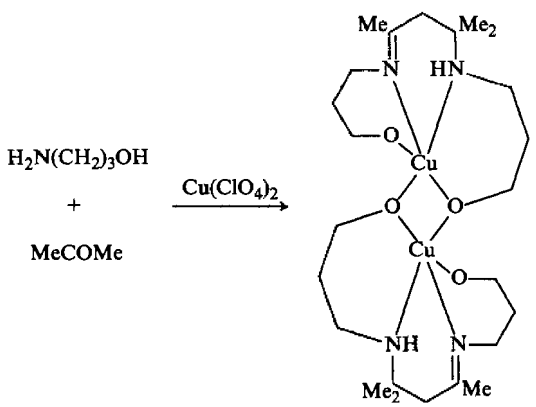


(9)

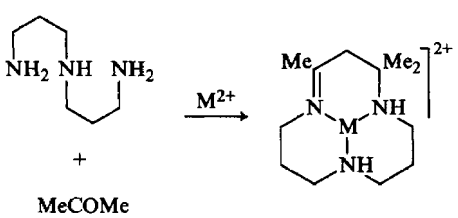


(10)

Variation in amines leads to the formation of some interesting products, as shown in equations (11)[88] and (12).[89]



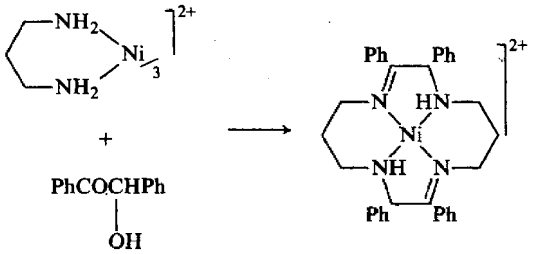
(11)



(12)

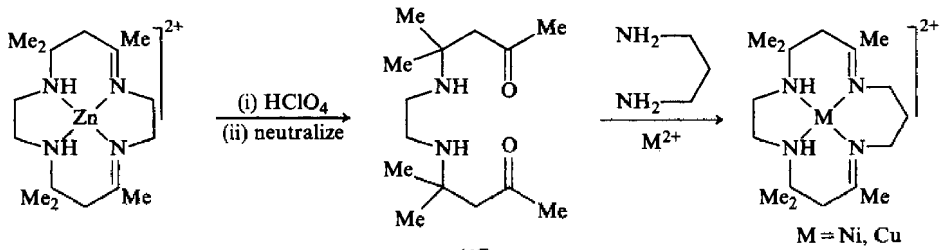
In many of the above examples, especially those resulting in the formation of macrocyclic complexes, the metal-free macrocycles can be obtained as hydroperchlorate salts by combination of the amino and carbonyl fragments in the presence of perchloric acid. Such a procedure has resulted in the formation of an even wider range of macrocyclic complexes than is available by metal template methods. The two approaches are complementary, as different geometrical isomers and stereoisomers can be formed by the different methods in some cases.

In the template reactions, acetone can be replaced by the preformed aldol, diacetone alcohol, and also the α,β-unsaturated ketone mesityl oxide.[90–93] The use of hydroxyketones can be extended to include benzoins, provided that the 1,3-diaminopropanenickel(II) complex is used (equation 13).[91]



(13)

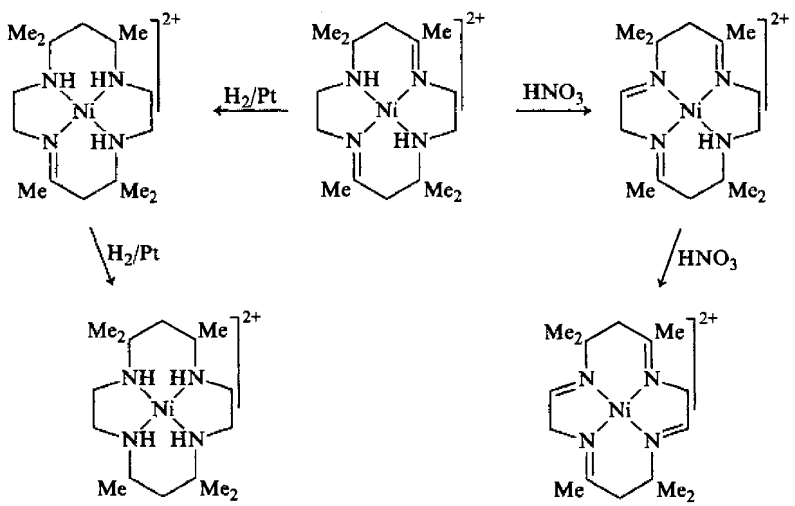
β-Amino imine complexes can also be synthesized from template reactions of β-amino ketones and amines. This approach has been applied to the amino ketone (**45**), which can be formed by acidic hydrolysis of a zinc(II) macrocyclic complex (Scheme 9).[94,95]



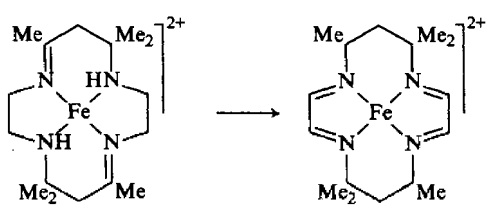
(**45**)

Scheme 9

Curtis-type macrocyclic complexes are sufficiently stable to undergo a variety of oxidation and reduction processes to yield a range of complexes containing from zero to four imine linkages (Scheme 10).[40,66,84,85,96] The oxidative dehydrogenation process is metal-ion dependent, as illustrated by the alternative ligand structure developed from the iron(II) complex (equation 14).[97,98]



Scheme 10



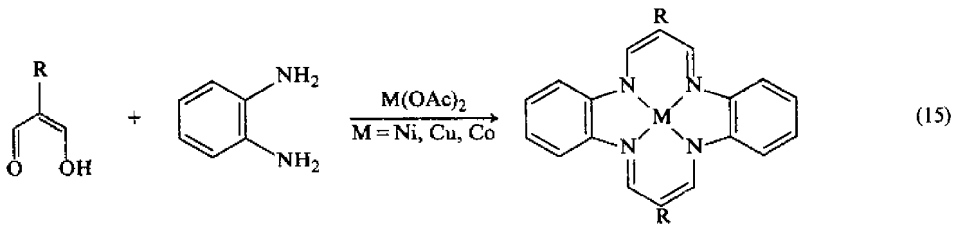
(14)

61.1.2.4 β-Diimines

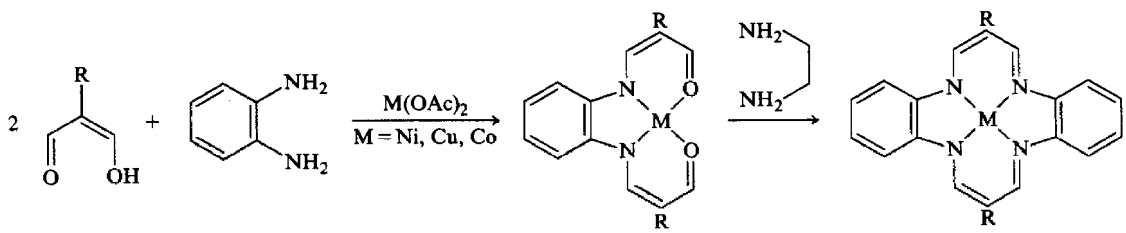
In this section, formation of ligands incorporating the β-diimine fragment will be considered. Such a fragment is usually enolized so that it is more accurately described as a β-amino-α,β-

unsaturated imine or as a vinylogous amidine. The related benzo analogs will also be included in this section.

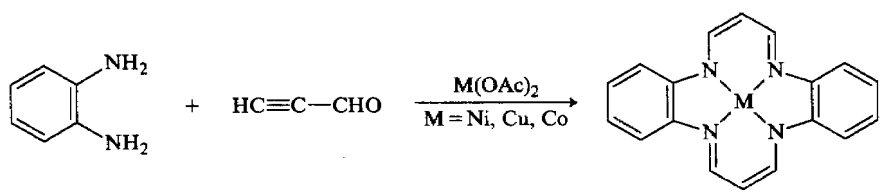
Template reactions between malonaldehydes and diamines in the presence of copper(II), nickel(II) or cobalt(II) salts yield neutral macrocyclic complexes (equation 15).[99–102] Both aliphatic[102] and aromatic[101] diamines can be used. In certain cases, non-macrocyclic intermediates can be isolated and subsequently converted into unsymmetrical macrocyclic complexes by reaction with a different diamine (Scheme 11).[101] These methods are more versatile and more convenient than an earlier template reaction in which propynal replaces the malonaldehyde (equation 16).[103] This latter method can also be used for the non-template synthesis of the macrocyclic ligand in relatively poor yield. A further variation on this reaction type allows the use of an enol ether (vinylogous ester), which provides more flexibility with respect to substituents (equation 17).[104] The approach illustrated in equation (15), and Scheme 11 can be extended to include reactions of β-diketones. The benzodiazepines, which result from reaction between 1,2-diaminobenzenes and β-diketones, can also serve as precursors in the metal template reaction (Scheme 12).[101,105,106] The macrocyclic complex product (**46**) in this sequence, being unsubstituted on the *meso* carbon atom, has been shown to undergo an electrochemical oxidative dimerization (equation 18).[107]



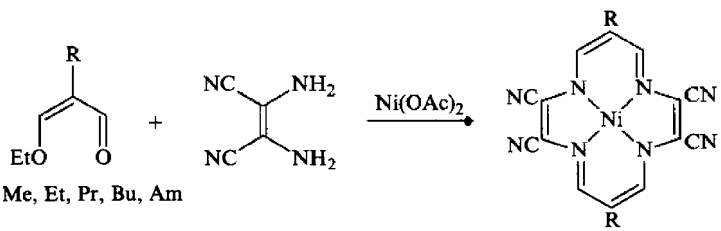
(15)



Scheme 11



(16)

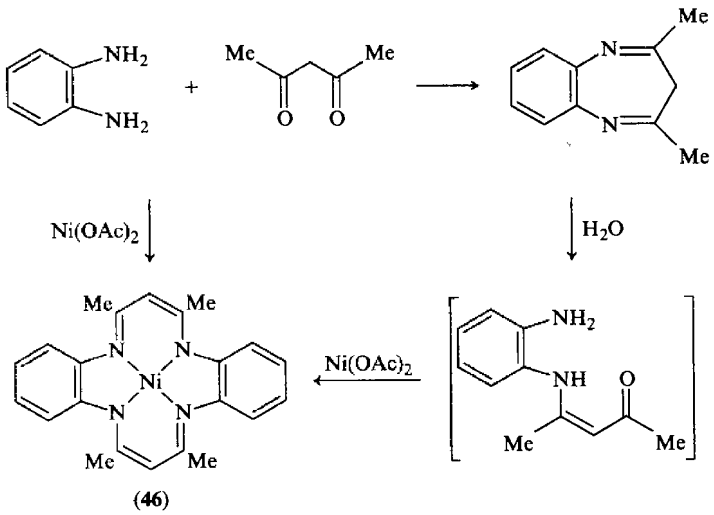


(17)

A single vinylogous amidine linkage has been incorporated into aliphatic macrocyclic complexes by template reactions (Scheme 13).[108–111] Normally, the complexes (**47**) are isolated, but under highly acidic conditions the protonated complexes (**48**) can be obtained.

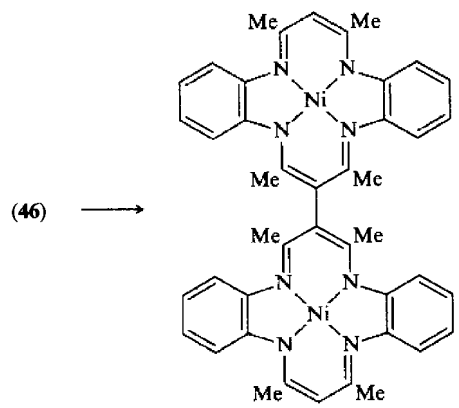
The nickel(II) complexes (**48**) can be catalytically hydrogenated to complexes containing a fully saturated macrocyclic ligand (equation 19).[112] Numerous studies of oxidative dehydrogenation of complexes (**47**) have been carried out and, in some cases, dimerization and oxygenation processes occur (Scheme 14).[113–115]

Macrocyclic complexes containing two vinylogous amidine linkages have been formed from ligands such as (**49**) which were generally prepared by non-template reactions. However, in an isolated example the free ligand (**49**) could be obtained in good yield by reaction of a nickel(II) complex of a vinylogous thioamide with 1,3-diaminopropane (equation 20).[116] A thorough

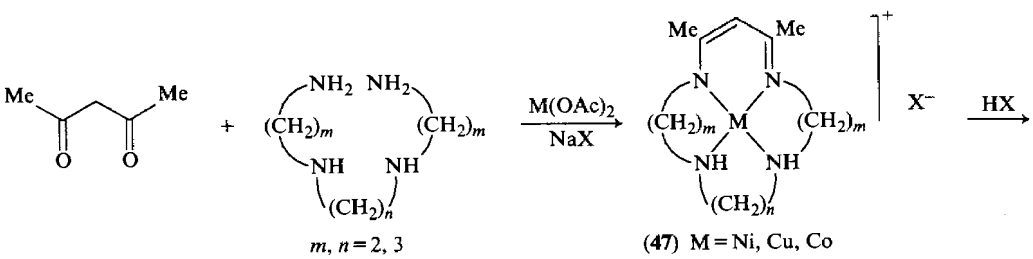


(46)

Scheme 12

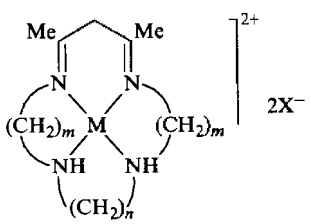


(18)



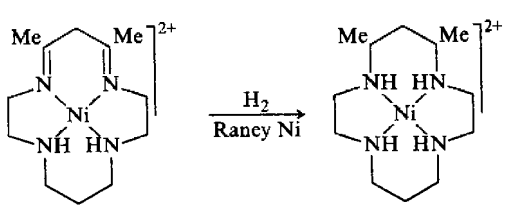
m, *n* = 2, 3

(47) M = Ni, Cu, Co

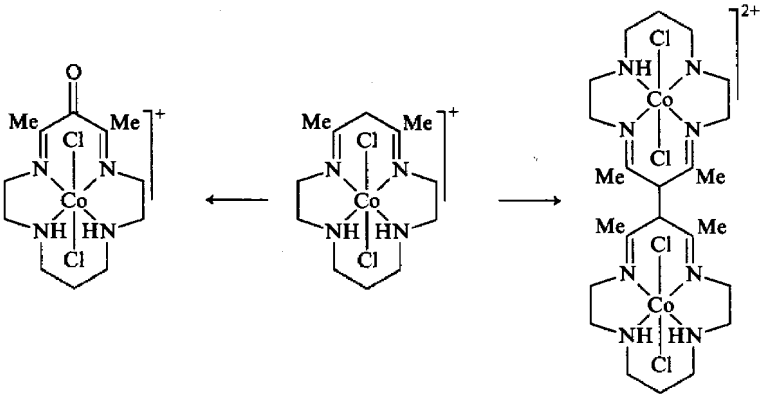


(48)

Scheme 13

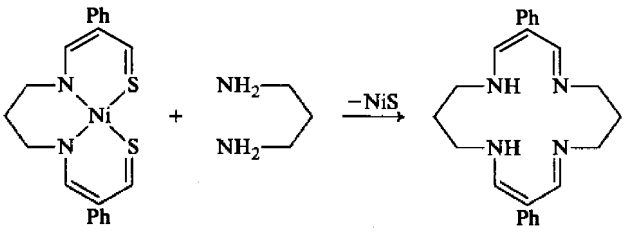


(19)



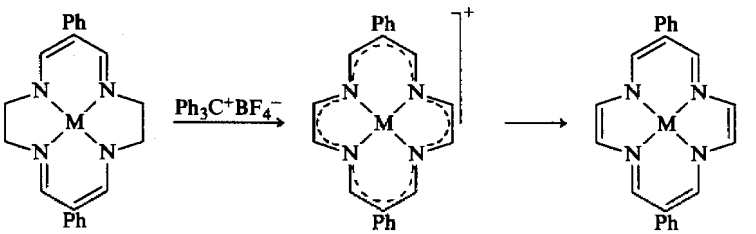
Scheme 14

investigation of the oxidative dehydrogenation of complexes such as (**49**) has been carried out,[117] and the results are summarized in Schemes 15 and 16.

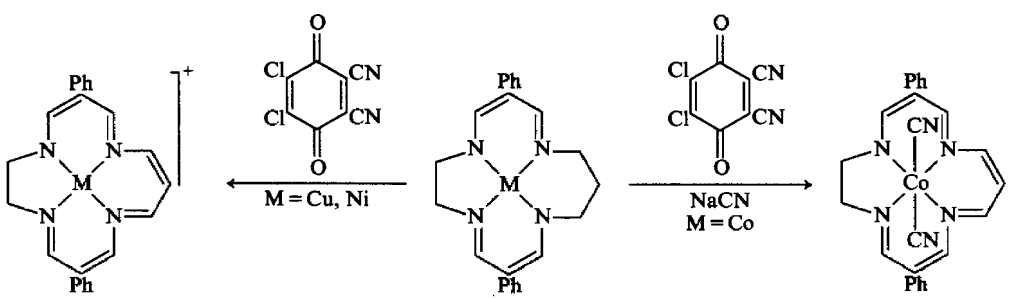


(20)

(**49**)



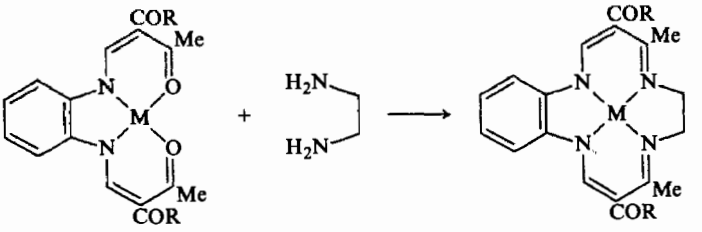
Scheme 15



Scheme 16

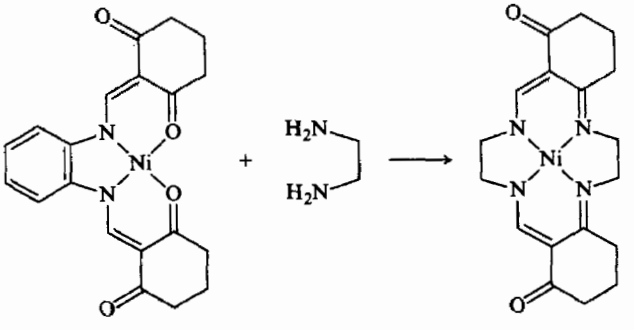
The reactivity of bis(acetylacetone)ethylenediimine metal(II) complexes towards diamines is quite poor, and macrocyclic complexes cannot be obtained, even from forcing conditions.[118] The carbonyl group loses reactivity by virtue of a delocalized vinylogous amide chromophore. This problem has been overcome by the introduction of a second carbonyl function, either in a ketone or ester group. Jäger has developed template reactions of this type and opened up an area of great importance. A general summary of the reactions is shown in equation (21).[119–121] Rather vigorous conditions are still required for these reactions and an indication is given by the decreased reactivity shown by complex (**50**) (equation 22).[122] 1,2-Diaminoethane not only reacts with the carbonyl groups to form imines, but it undergoes Michael addition leading to amine exchange. 1,2-Diaminobenzene, in contrast, does not react with complex (**50**). Improved reaction conditions, resulting from mechanistic studies, have been published for the template preparation of Jäger-type macrocyclic complexes.[123]

One of the most valuable synthetic aspects of the Jäger-type ligands is the presence of the acetyl substituent. Not only does this offer an important activating feature in the template formation of the macrocycle, but it also offers a functional group which can be manipulated by further



(21)

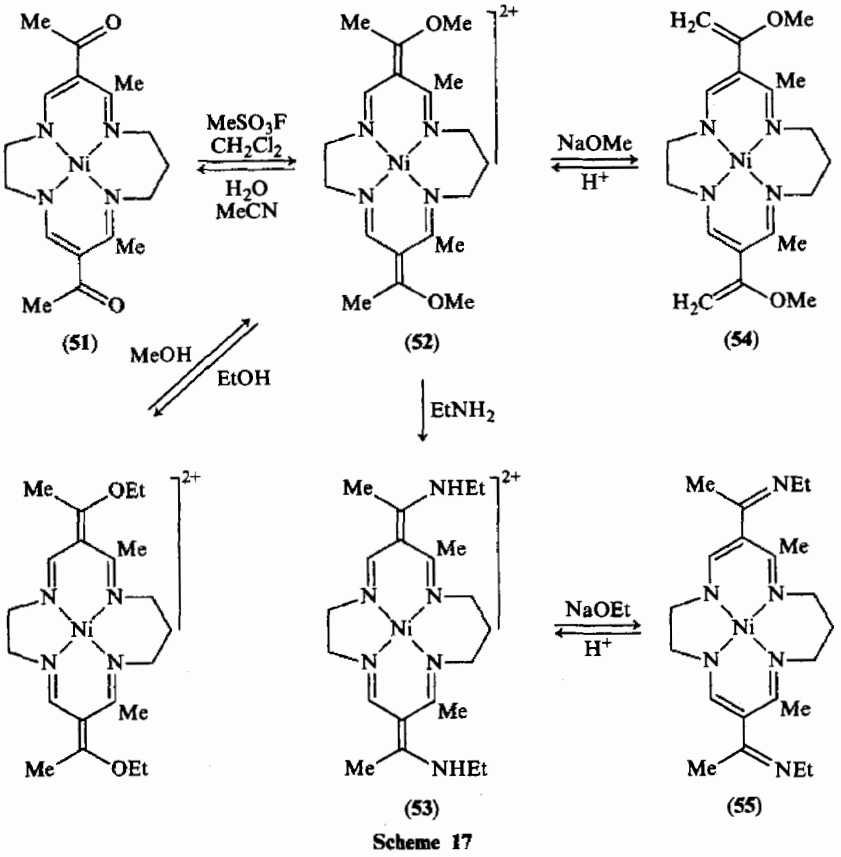
M = Ni, Cu
R = Me, Ph, OEt



(22)

(50)

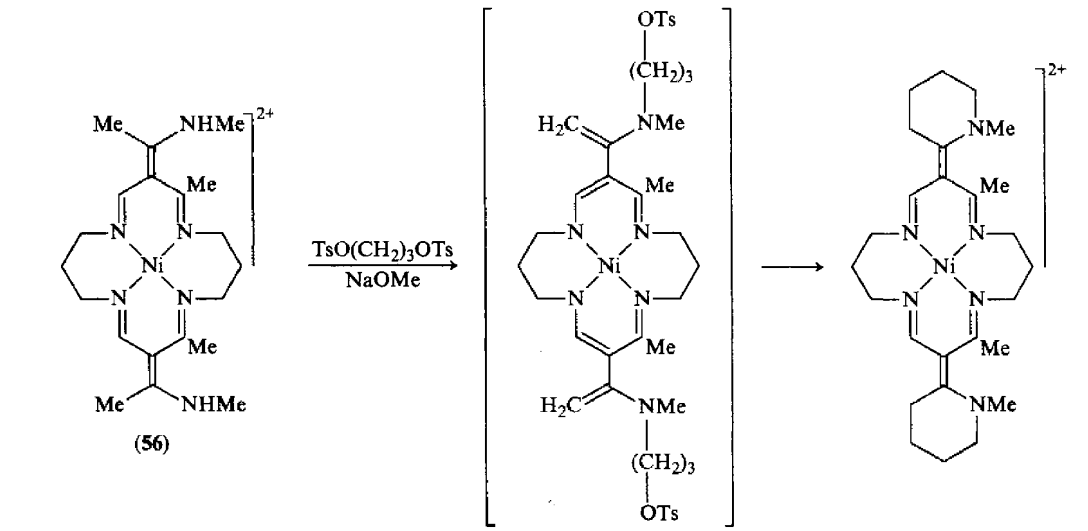
synthetic transformation. Busch and coworkers have made very valuable use of this feature. The acetyl group is initially activated by methylation with methanefluorosulfonate to give an enol ether which is susceptible to attack by nucleophiles such as water, alcohols and amines (Scheme 17).[124,125]



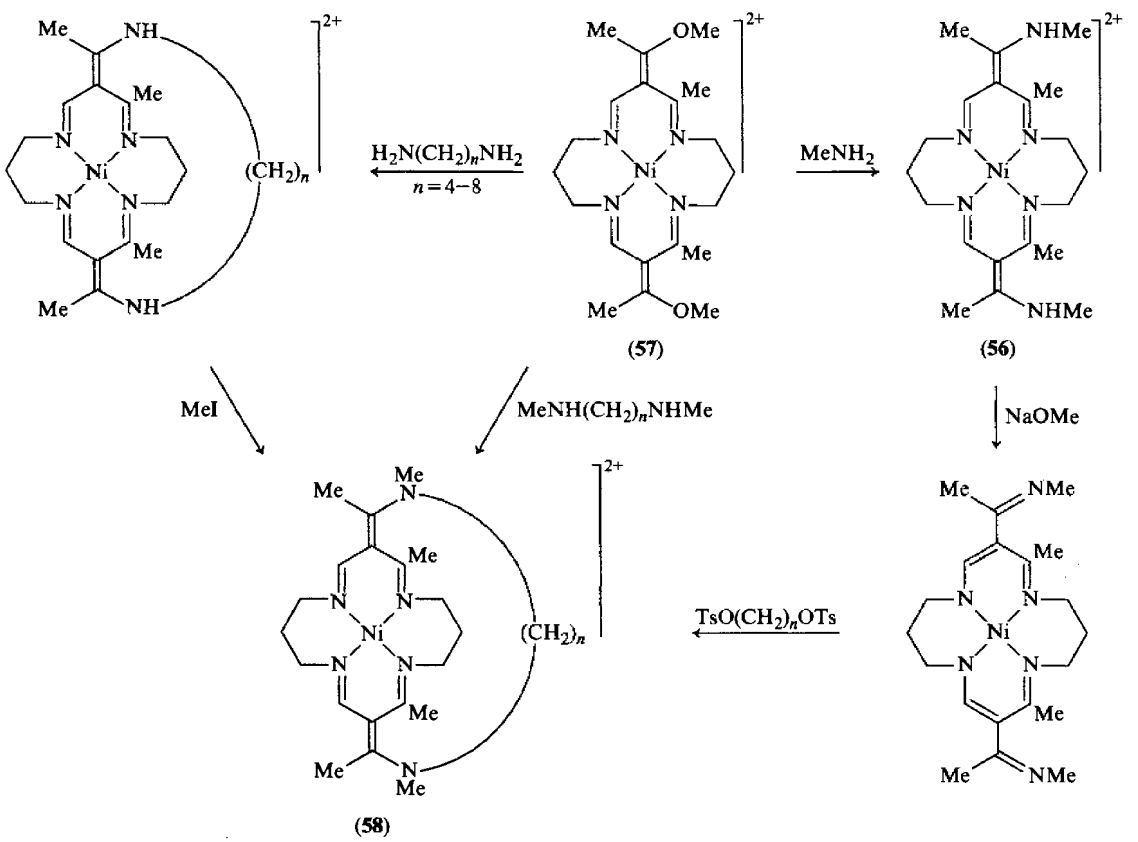
Scheme 17

While most of the work has been done commencing with the nickel(II) complex (**51**), the chemistry is quite general. The enamine complex (**53**) can be deprotonated on nitrogen to yield the neutral imine complex (**55**). Even the protons of the methyl group in the enol ether complex (**52**) are sufficiently acidic for the formation of the neutral complex (**54**). Both of these reactivity features occur together in the alkylation reaction shown in Scheme 18.[126] The macrocyclic rings in complexes such as (**52**), (**53**) and especially the more flexible complex (**56**) are not planar but bowl-

shaped. As a consequence, it is a straightforward matter to link the two exocyclic nitrogen atoms of compound (**56**) by intramolecular alkylation.[126] The same types of linked products (**58**) can be obtained from enol ether complexes (**57**) by treatment with a diamine.[127] Both sequences are exemplified in Scheme 19. A more recent example involves alkylation of nitrogen atoms more distantly removed from the macrocyclic ring (equation 23).[128] Furthermore, two macrocyclic complexes can be linked together in larger macrocycles such as compound (**59**).[129]

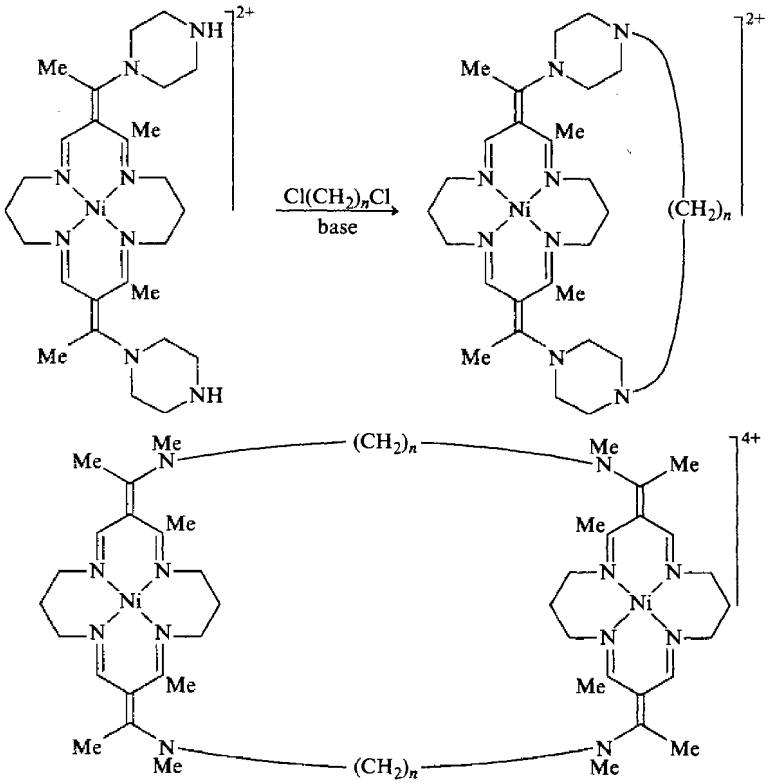


Scheme 18



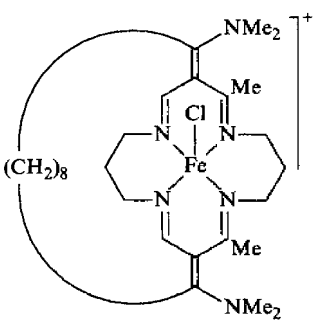
Scheme 19

The nickel(II) ions can be removed from the above range of macrocyclic complexes and the resulting free ligands can then be converted into iron(II) complexes, [130] which have been shown to exhibit reversible oxygen binding.[131,132] Similar characteristics have been observed for iron(II) complexes such as (**60**), which contain bridging from methyl carbon atoms rather than nitrogen atoms.[132] Synthetic information has not been disclosed, but several routes are possible.



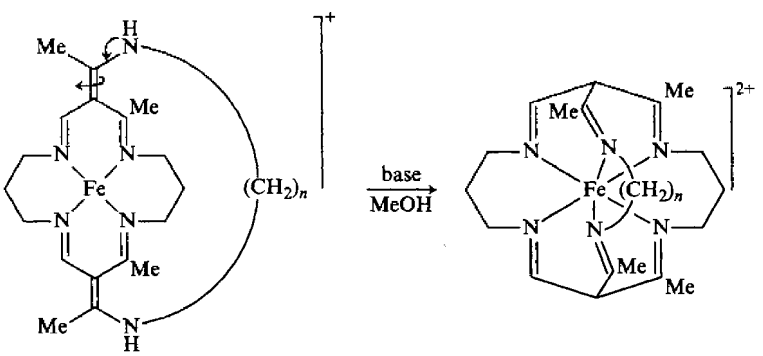
(23)

(59)



(60)

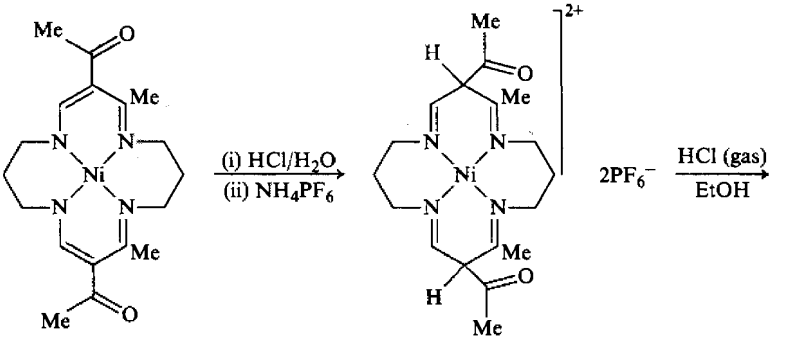
Certain iron(II) complexes, on treatment with strong base, undergo an interesting tautomerism which results in a change of ligand geometry and formation of clathrochelate structures (equation 24).[133]

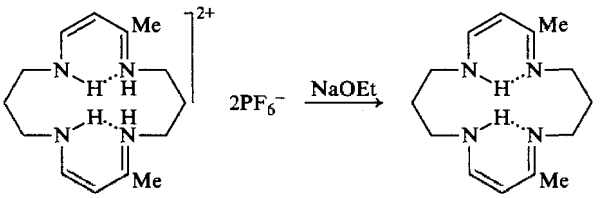


(24)

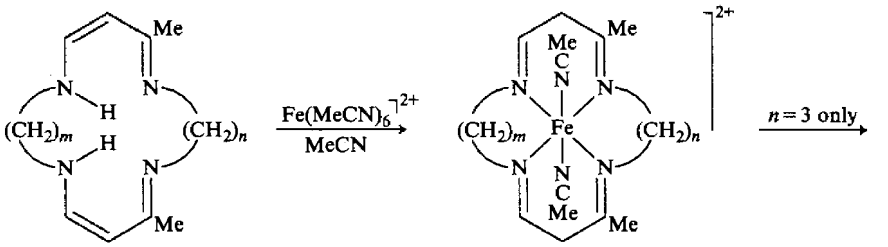
$n = 2, 5, 6$

The original Jäger-type complexes can be deacylated by treatment with acid: demetallation follows and the free macrocycles can be isolated (Scheme 20).[134] These can be converted into iron(II) complexes with acetonitrile coordinated in the axial positions. However, these are unstable in the example with 15- and 16-membered rings and undergo cyclization as a result of carbanion attack on the coordinated acetonitrile (Scheme 21).[134–136] A similar reaction occurs with the cobalt

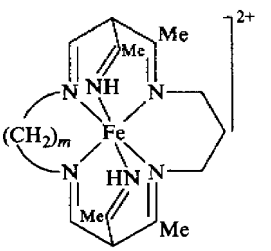




Scheme 20



m, *n* = 2, 3



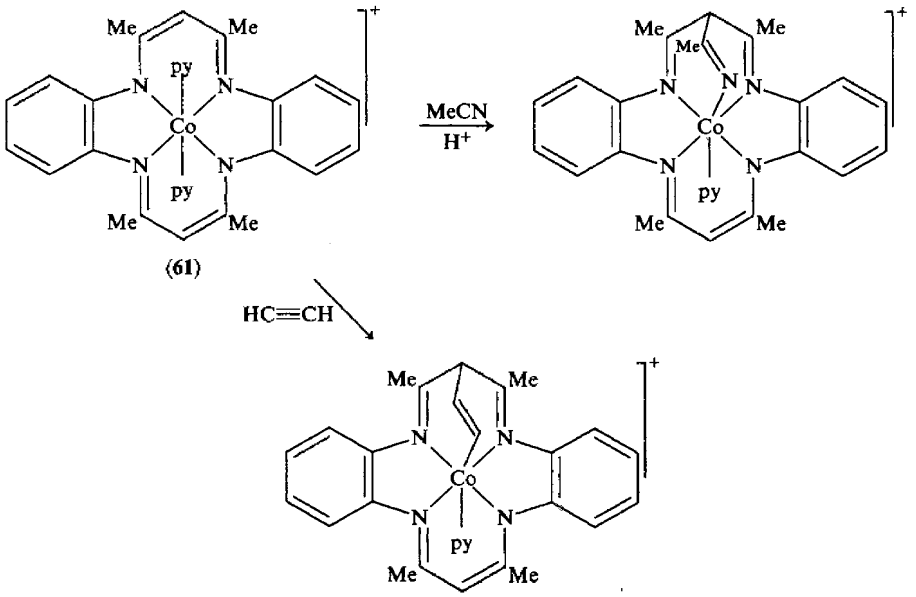
Scheme 21

complex (**61**), as does a related organometallic cyclization of coordinated acetylene (Scheme 22).[137,138]

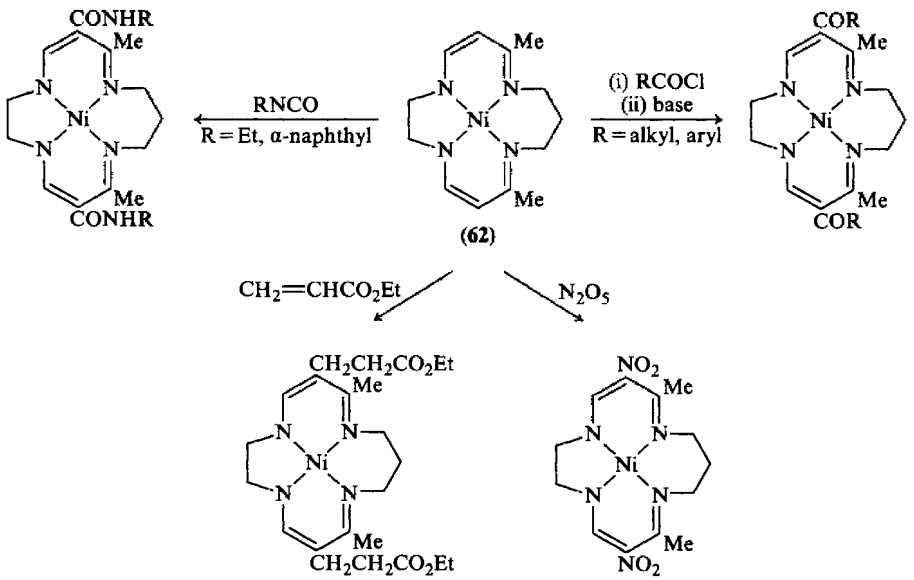
The deacylated Jäger-type complexes (**62**) can be reacylated with a variety of groups and also undergo nitration and addition to isocyanates and α,β-unsaturated esters (Scheme 23).[139,140]

Complexes such as (**62**) can be submitted to hydrogenation and oxidative dehydrogenation processes of the type already described for related systems. The most interesting investigation has actually been carried out on complexes of a tetramethyl substituted ligand prepared from a non-template reaction sequence. In particular, oxidative dehydrogenation affords macrocyclic chromophores with six and seven double bonds (Scheme 24).[118,141]

Jäger solved the problem of low reactivity in vinylogous amide chromophores by the introduction of an additional carbonyl group. An alternative solution involves the incorporation of the double bond in a benzene ring. This gives rise to 2-aminobenzaldehyde derivatives, which exhibit both amino and carbonyl reactivity. This has been demonstrated by the trimerization and tetramerization reactions under the influence of metal ions to produce highly conjugated macrocyclic complexes (**66**) and (**67**) respectively (Scheme 25).[142,143] In the absence of metal ions the polycyclic products (**63**) and (**64**) are formed, but these can generally be converted by metal ions into the complexes (**66**) and (**67**) respectively.[144] An exception is presented by copper(II) ions, which convert compound (**63**) into the quadridentate complex (**67**).[145] In concentrated acid, 2-aminobenzaldehyde yields the salt (**65**) which undergoes metal-promoted rearrangement to the macrocyclic complex



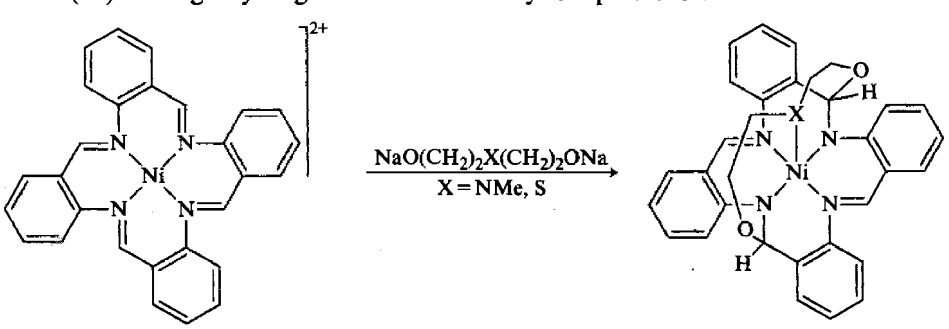
Scheme 22



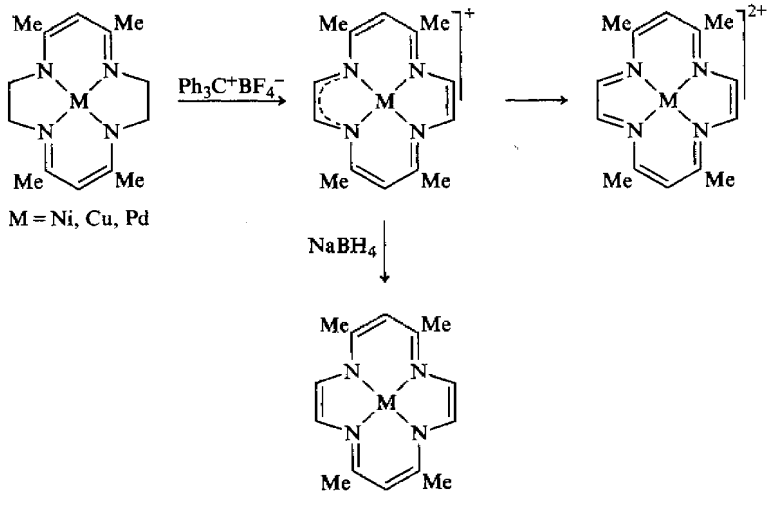
Scheme 23

(**67**).[146] Complexes of nickel(II), copper(II), cobalt(III), zinc(II), iron(II), palladium(II), platinum(II) and vanadyl can be obtained. Although the reaction sequence is fairly general for metal ions, it is not easily extendable to substituted 2-aminobenzaldehydes. However, 2-amino-5-methylbenzaldehyde has recently been used successfully in the macrocyclization reaction.[147]

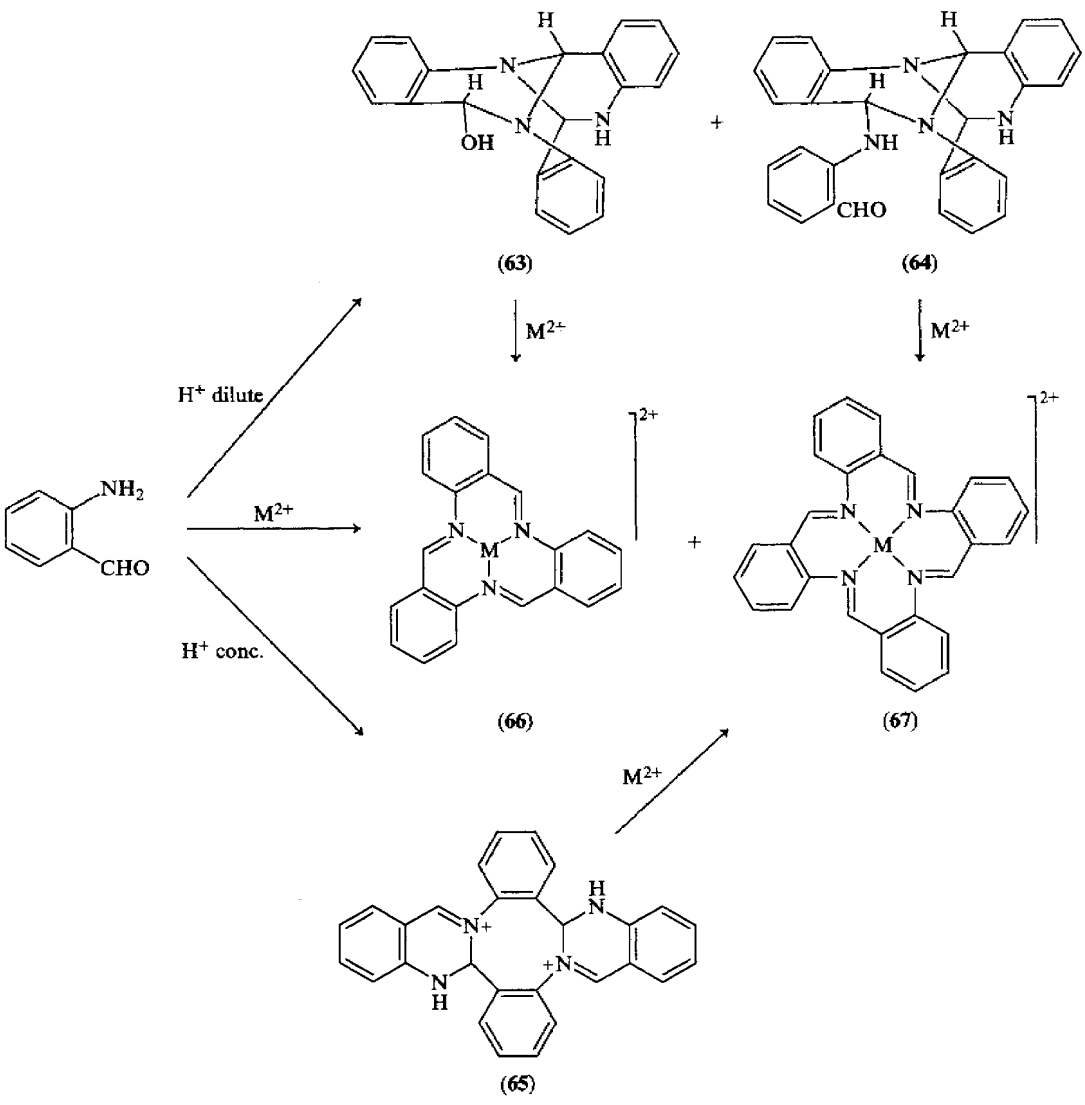
Although the macrocyclic complexes (**67**) are very stable to hydrolysis they are susceptible to attack by nucleophiles, as exemplified in equation (25).[148–151] The nickel(II) and copper(II) complexes (**67**) undergo hydrogenation at relatively low pressures.[152]



(25)



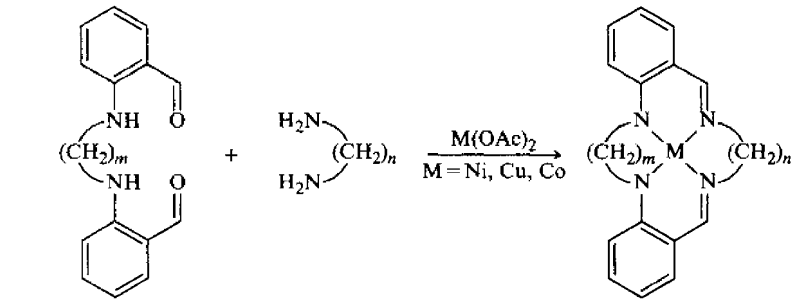
Scheme 24



Scheme 25

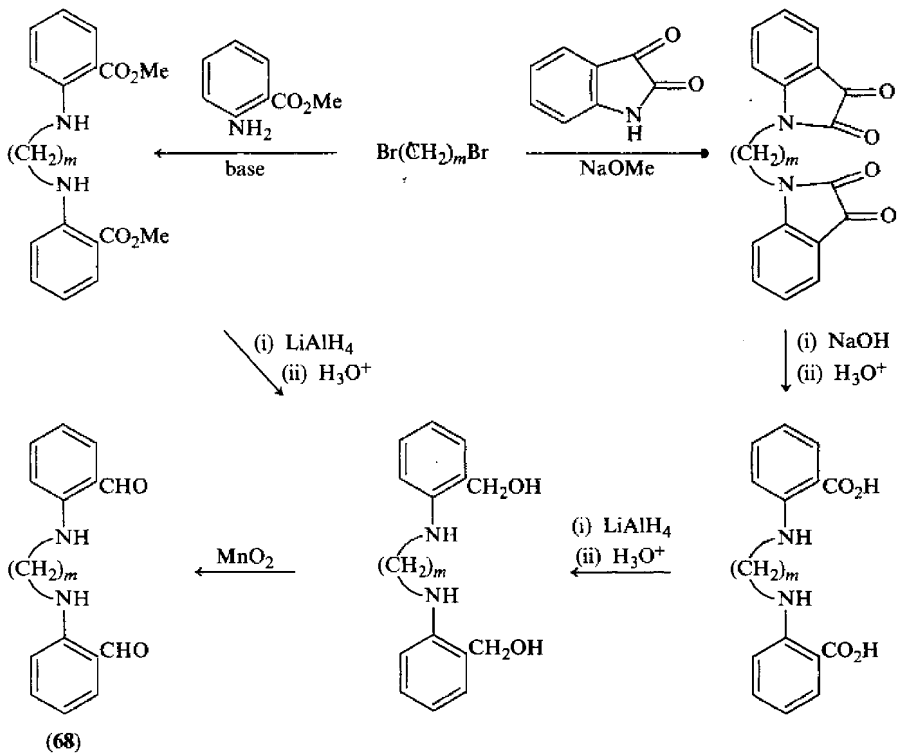
2-Aminobenzaldehyde structural fragments have been incorporated into diaminodialdehydes, which can act as precursors for macrocyclic complexes. The initial work in this area involved template reactions between dialdehydes and diamines in the presence of hydrated metal(II) acetates in methanol (equation 26).[153–155] Benzene-1,2-diamines could also be used in these syntheses.

Although the metal ions promoted macrocycle formation, in some cases the free macrocycles could be synthesized in non-template conditions of high dilution. The free macrocycles have sometimes been prepared by means of template reactions involving zinc(II) acetate. The dialdehydes (**68**) were prepared by a sequence of reactions involving a poor initial alkylation step, but a superior approach has been developed (Scheme 26).[156–158] Alkylation of isatin compounds can be carried out in high yield and substituted isatins are readily available.



(26)

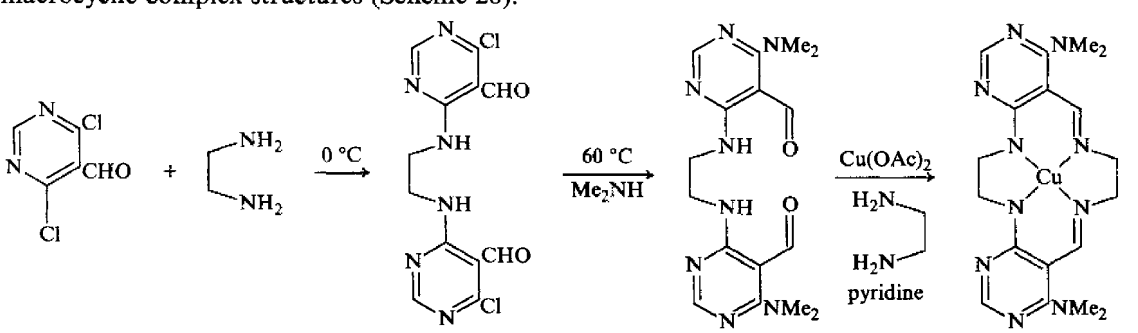
(**68**) $n, m = 2, 3$



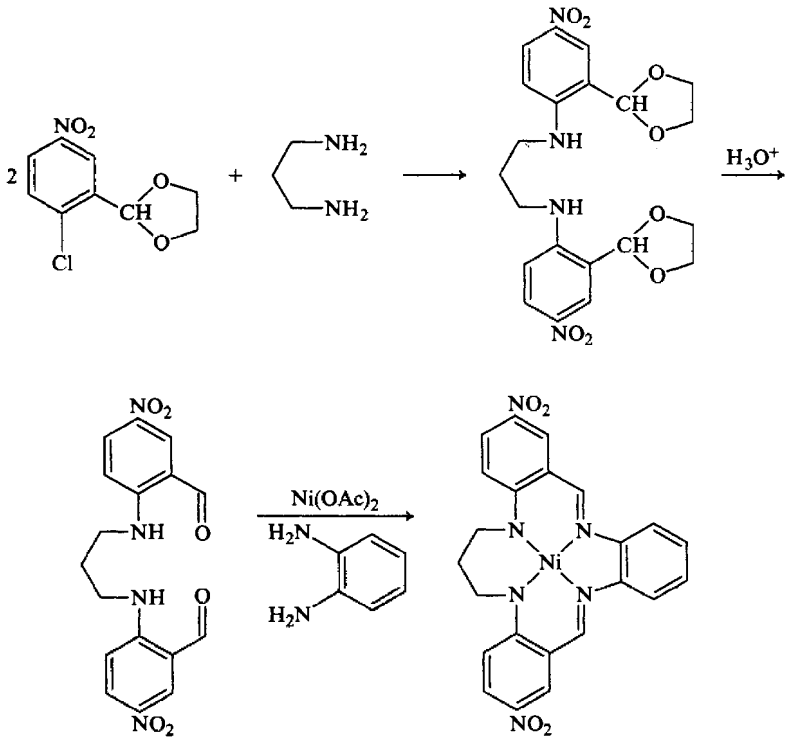
(**68**)

Scheme 26

An early approach to suitable dialdehydes made use of a nucleophilic aromatic substitution process which enabled the synthesis of nitro-substituted complexes to be achieved (Scheme 27).[159,160] Very recently, a similar approach has been used to incorporate pyrimidine rings into macrocyclic complex structures (Scheme 28).[161]

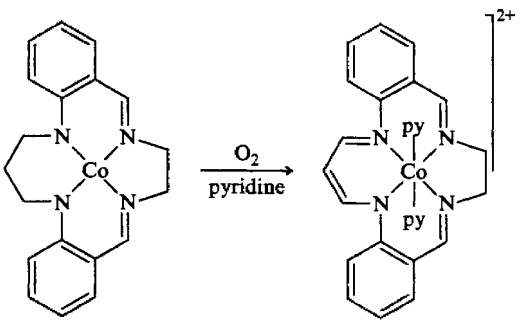


Scheme 28

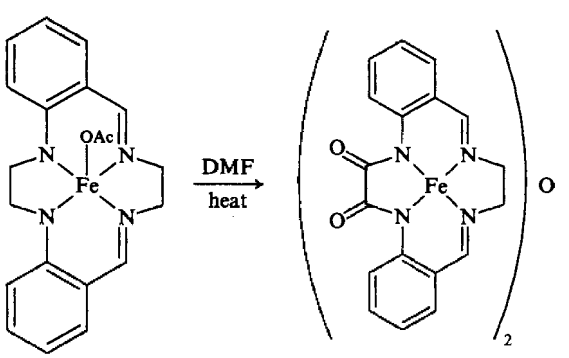


Scheme 27

Propano-linked macrocyclic complexes (**69**) have been shown to undergo oxidative dehydrogenation with ease under mild conditions (equation 27).[157,162] This reaction occurs for nickel(II), copper(II) and cobalt(II) complexes and leads to cobalt(III) 'dibenzocorromins', which are simple models of the vitamin B_{12} coenzyme nucleus.[163] Macrocyclic complexes containing this ligand chromophore had already been prepared by a direct metal template method (Scheme 29).[164,165] However, the oxidative dehydrogenation route offers greater experimental certainty and variety.

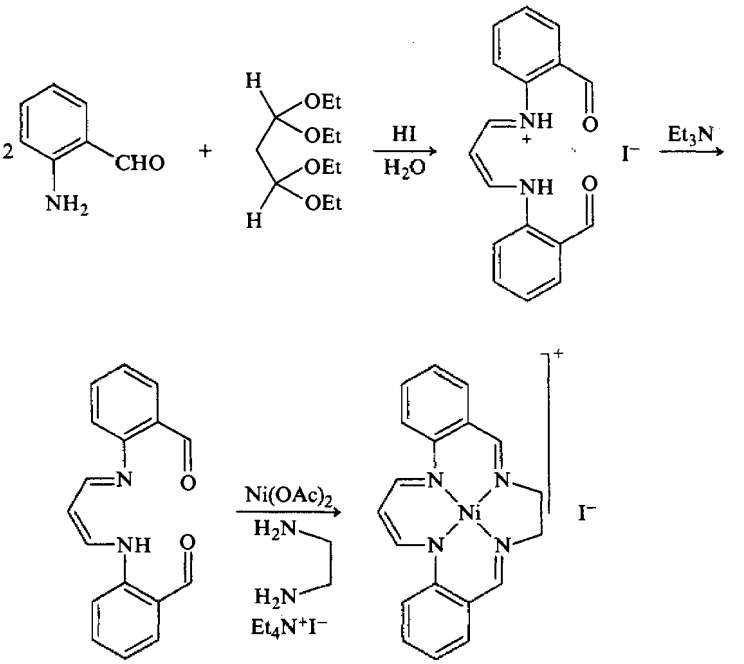


(69) (27)

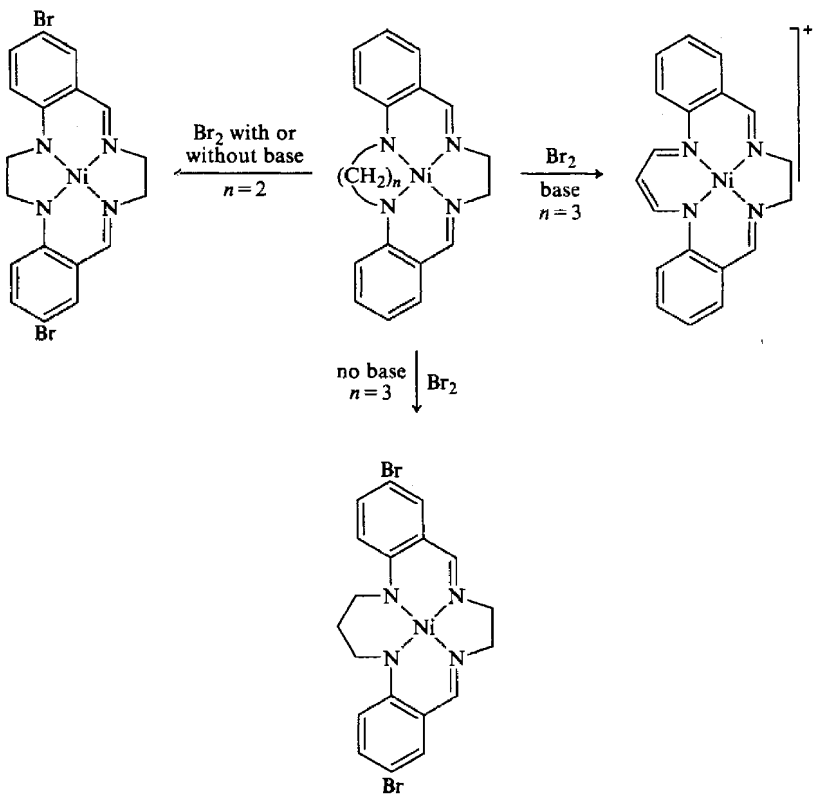


(28)

During studies on the oxidative dehydrogenation of complexes such as (**69**), it was discovered that ring bromination could occur when bromine was used as the oxidizing agent. Reaction conditions could be varied so as to optimize either reaction (Scheme 30).[157] Oxidative dehydro-



Scheme 29

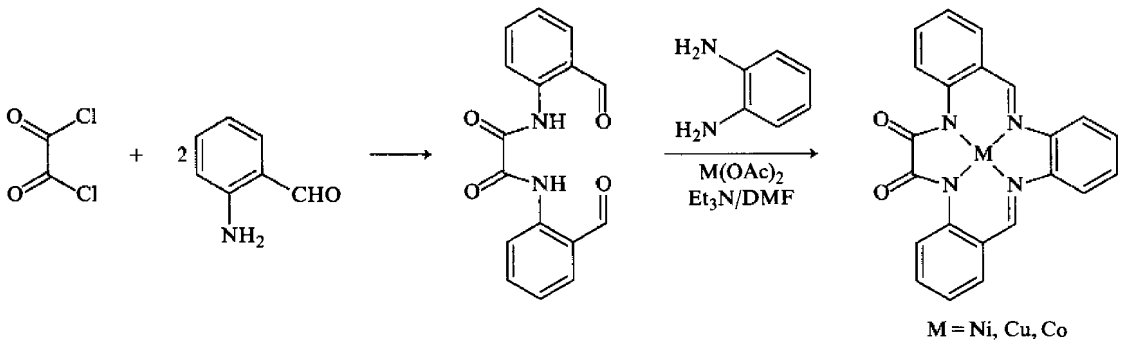


Scheme 30

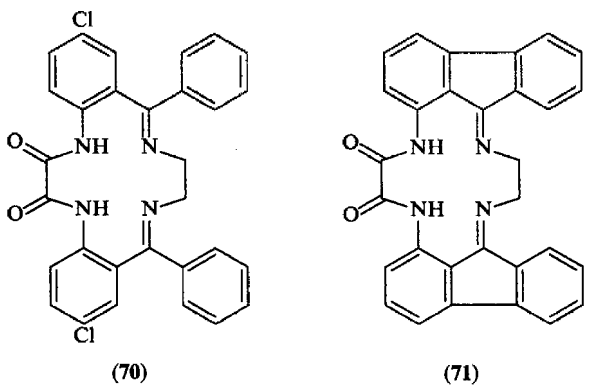
genation products could not be obtained from ethano-bridged complexes, so bromination occurred exclusively. Oxygenation of an ethano bridge has been reported (equation 28).[166]

The construction of suitable dialdehydes for macrocycle formation by metal template methods has more recently been extended to include a range of oxamides. In the first case, the simple 2,2′-(oxalyldiimino)bisbenzaldehyde underwent rather sluggish template reactions but yielded extremely stable macrocyclic complexes (Scheme 31).[167,168] These products could be sulfonated in oleum, without destruction of the macrocyclic structure. This general synthetic route has been extended to include reactions of diketones and the formation of complexes of macrocyclic ligands such as (**70**) and (**71**). Attempts to incorporate a malonamide fragment in place of the oxamide

bridge have met with only limited success. The central carbon atom of the malonamide bridge must be fully substituted, and the diketone (**72**) serves as a suitable precursor for macrocyclic metal complex formation.[169] However, the cyclopropane analog (**73**) does not, but undergoes decomposition under the template reaction conditions. The diketones (**74**) with benzylidene malonate backbones gave rise to compounds with 11-membered rings, which seem to arise by a template pinacol reaction (equation 29).[169]

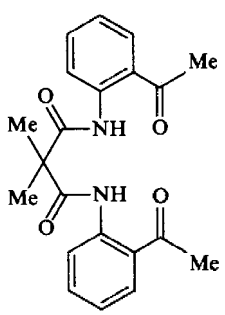


Scheme 31

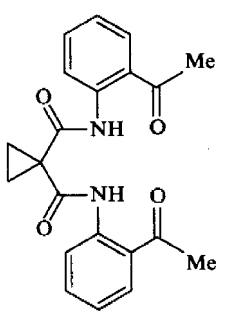


(**70**)

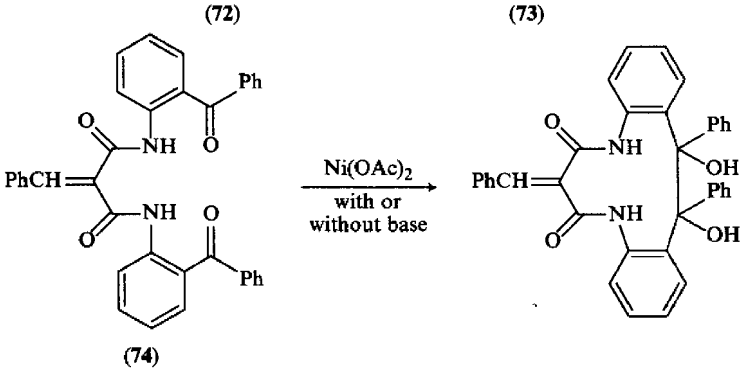
(**71**)



(**72**)



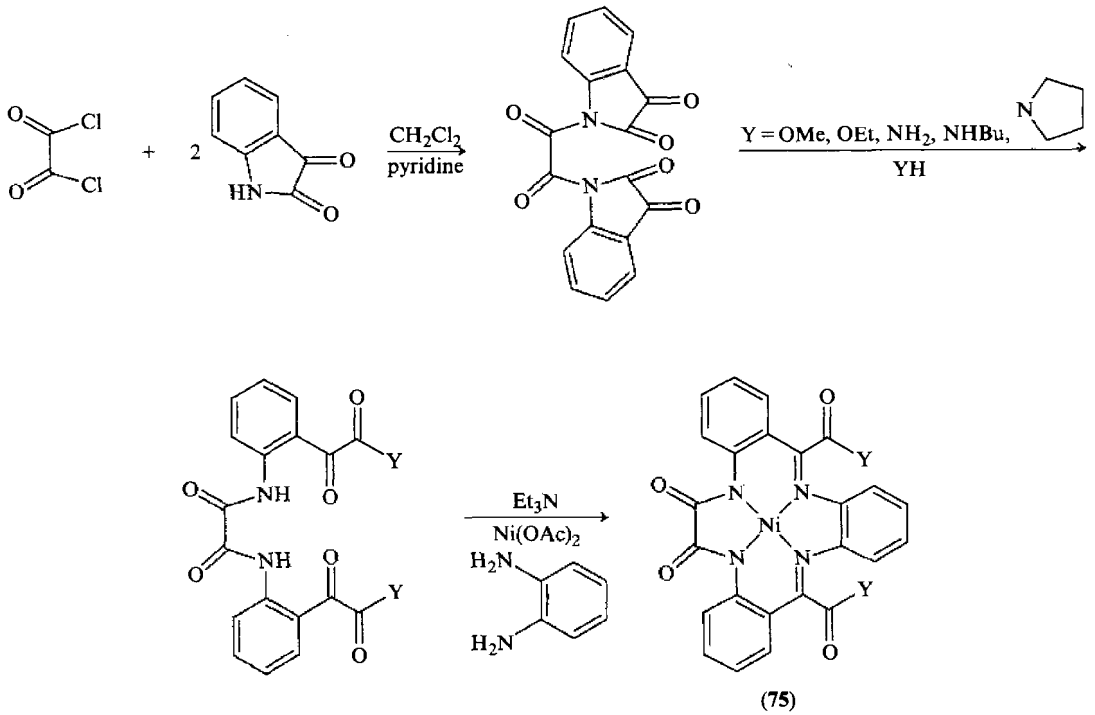
(**73**)



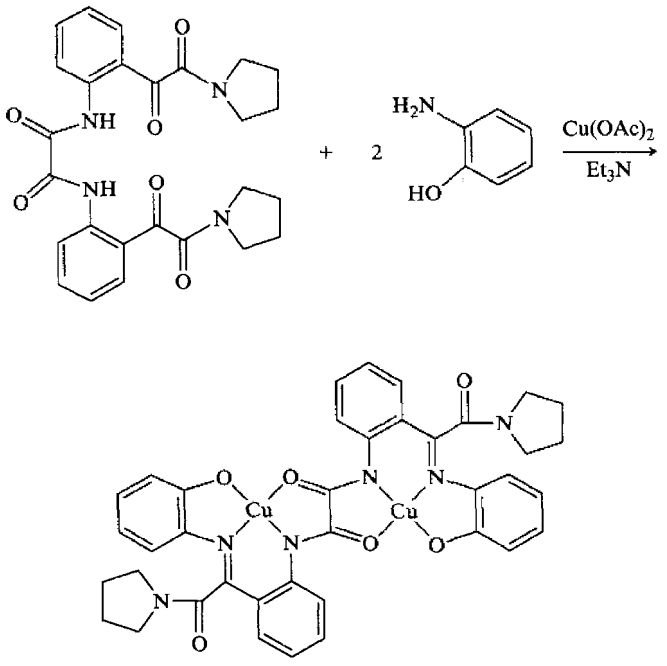
(**74**) (29)

An extremely versatile and simple synthesis of macrocyclic amide complexes has been based on the reactivity of *N*-acylisatin compounds (Scheme 32).[170] The template reaction occurs very readily as a result of the increase in electrophilicity of the carbonyl groups in the α-keto esters and

amides (**75**) compared with the parent aldehyde (*cf.* Scheme 31). The macrocycle precursors (**75**) can also lead to binuclear complexes in a template reaction (equation 30).[171]

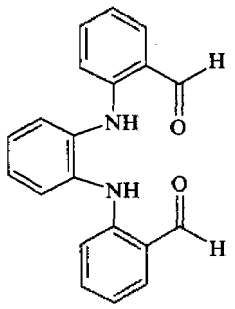


Scheme 32

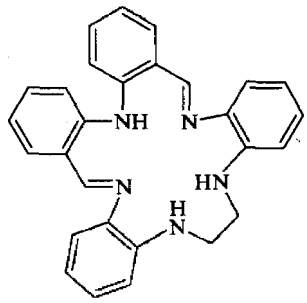


(30)

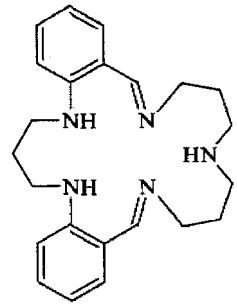
The dialdehyde (**76**) has been synthesized but does not undergo template reactions to give macrocyclic complexes.[61] This resistance to reaction possibly arises from the decreased reactivity of the formyl groups as a result of intramolecular hydrogen bonding. In contrast, the diformyldiphenylamine (**30**) readily yields macrocyclic complexes in template reactions, and this has been considered earlier (see equation 6). Dialdehydes such as (**30**) and (**68**) do not only lead to quadridentate macrocyclic complexes but also give quinquedentate and sexadentate complexes of ligands such as (**77**),[61] (**78**),[172] (**79**) and (**80**).[173,174] The ligands can often be removed from the complexes by treatment with pyridine in acetone.



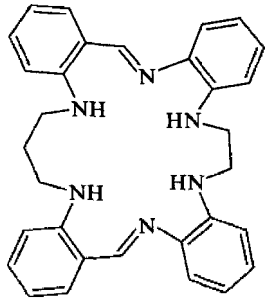
(76)



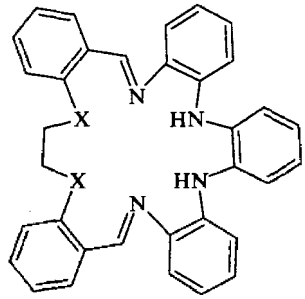
(77)



(78)



(79)

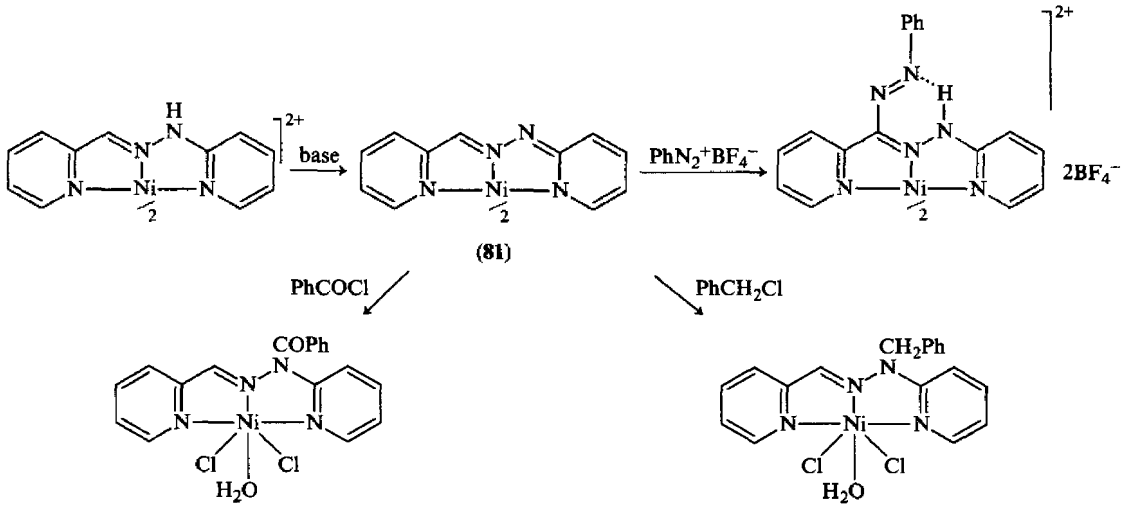


(80) X = NH, O, S

61.1.2.5 Hydrazones and Azines

Thermodynamic template reactions allow the formation of hydrazones from hydrazines and carbonyl compounds, in the same manner as simple imines are formed. However, in many cases it is more convenient to form hydrazones in non-template reactions, as they are generally easier carbonyl derivatives to isolate than are simple imines. Hydrazone complexes often are capable of further manipulation and both aspects of synthesis and reactivity will be combined in this section.

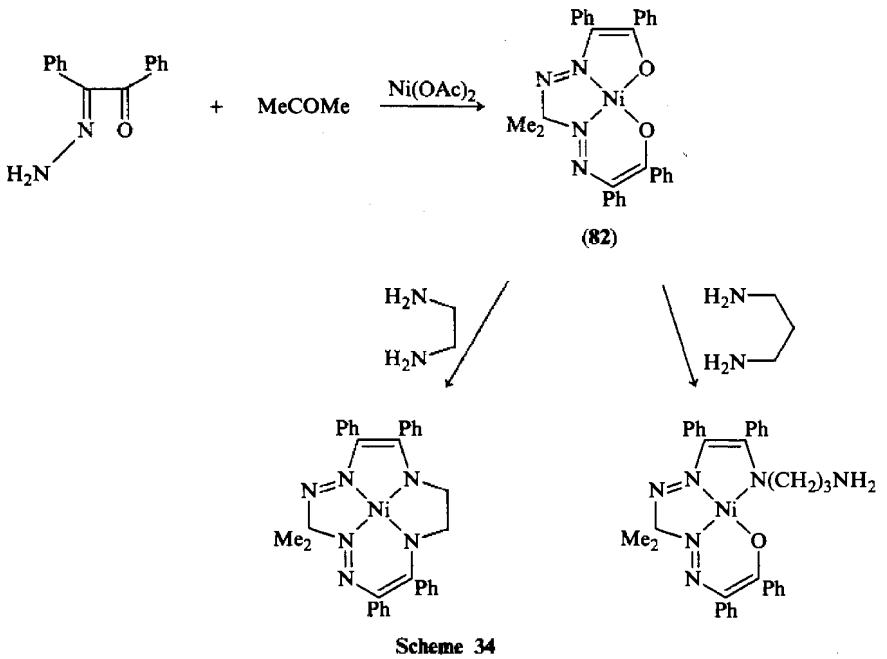
The 2-pyridylhydrazone of pyridine-2-carbaldehyde yields tridentate metal complexes which can be deprotonated to neutral complexes (**81**).[175–177] These in turn can be reprotonated, alkylated or acylated on nitrogen and reacted with benzenediazonium fluoroborate on carbon (Scheme 33).[178]



Scheme 33

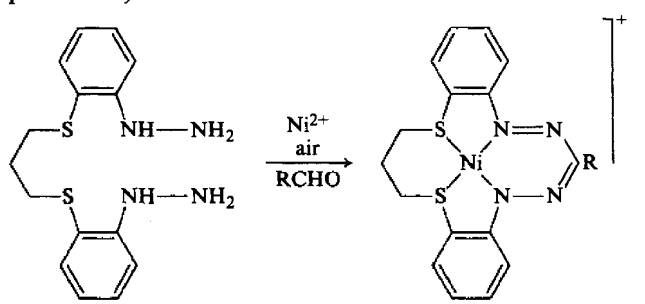
The monohydrazones of α-diketones react with acetone and nickel(II) acetate to give azine complexes (**82**), which can be converted to macrocyclic complexes by reaction with 1,2-diaminoethane, but not 1,3-diaminopropane (Scheme 34).[179–181]

Template reactions of a bis(hydrazine) and a bis(hydrazone) occur with nickel(II) ions and aldehydes or ketones (equations 31 and 32).[182,183] When aldehydes are used, oxidation occurs to give unsaturated chelate rings. A similar template reaction occurs with oxalyl dihydrazide and

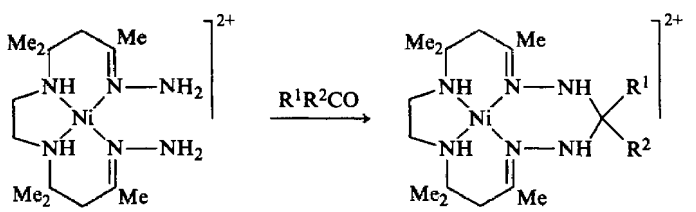


Scheme 34

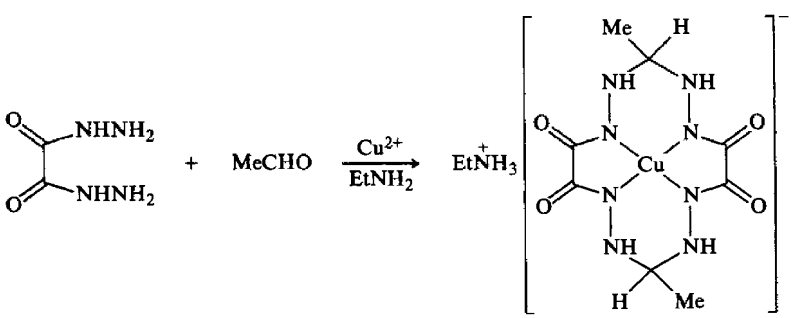
formaldehyde in the presence of copper(II) ions. Again, oxidation occurs and a copper(III) complex is formed (equation 33).[184,185]



(31)

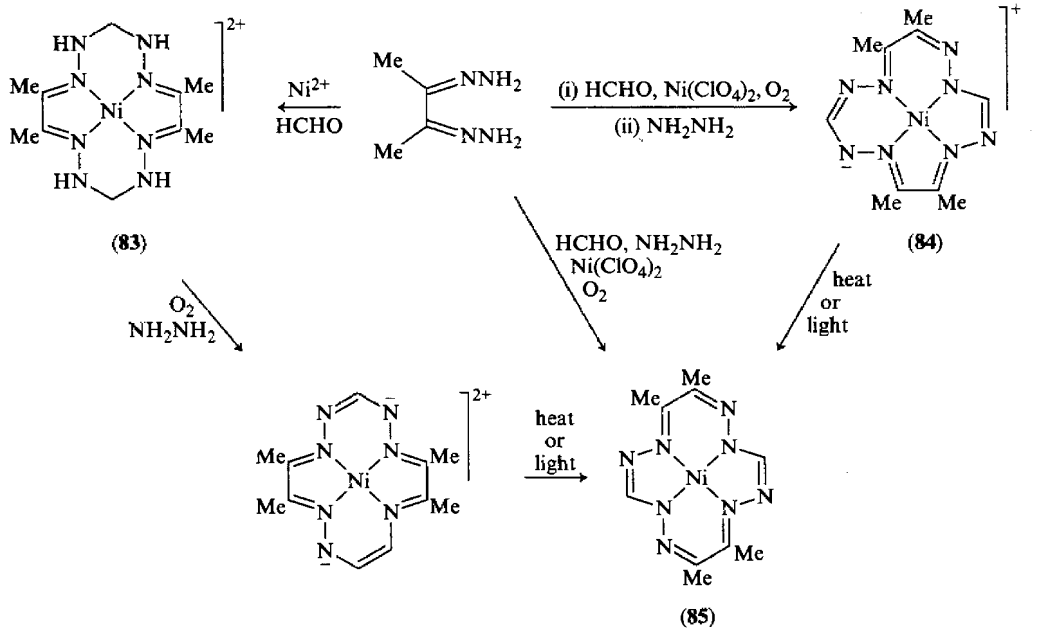


(32)



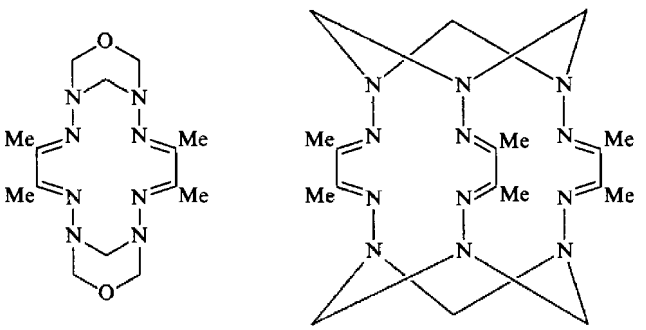
(33)

Dihydrazones of α-diketones can also undergo metal-controlled coordination with formaldehyde to yield the nickel(II), iron(II), cobalt(II) or copper(II) complexes (**83**). Reaction of these dihydrazones with nickel(II) perchlorate under oxidative conditions gives either (**84**) or the more stable (**85**) depending on the sequence of addition of reagents. Further transformations involving changes of ligand geometry are shown in Scheme 35.[186–188] The ligand of complex (**83**) is capable of further reaction with formaldehyde to yield complexes of ligand (**86**). Similar reaction with another molecule of dihydrazone and formaldehyde yields complexes of the more complex ligand (**87**). Iron(II), cobalt(II) and nickel(II) complexes of both (**86**) and (**87**) can be prepared.



(83) (84) (85)

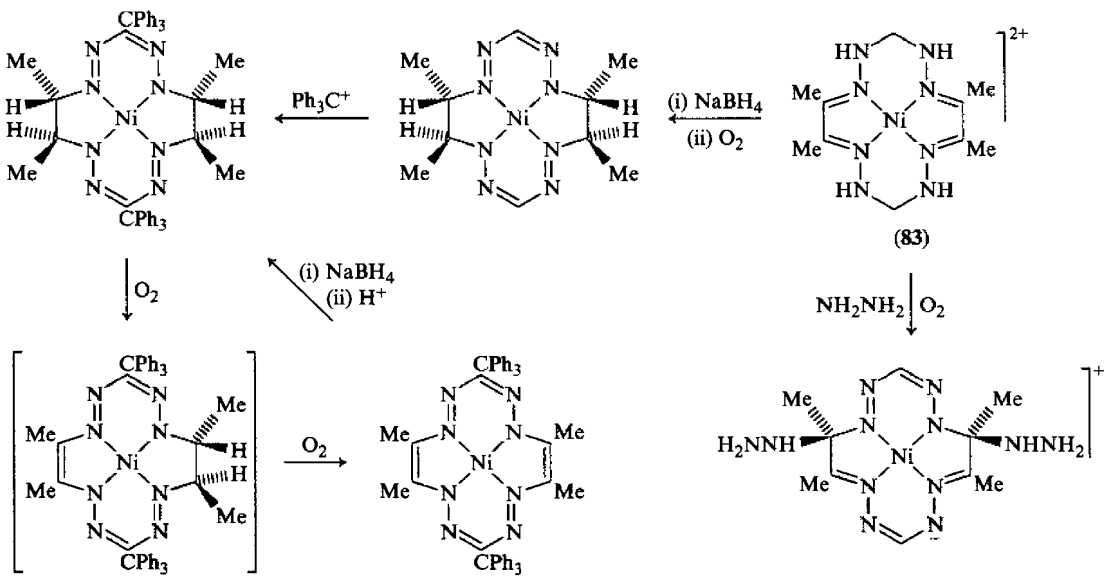
Scheme 35



(86) (87)

The metal-promoted reactions of 1,2-dihydrazones with formaldehyde (see Scheme 35) can be compared with the purely organic reactions of 1,2-dihydrazones with orthoesters, which lead directly to macrocyclic compounds from which complexes of structural type (**85**) can be prepared.[189,190]

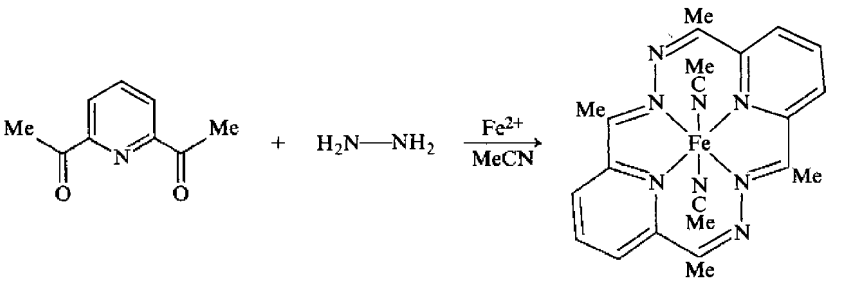
The octaazamacrocyclic complex (**83**) is capable of undergoing numerous transformations to give complexes with different patterns of ligand unsaturation (Scheme 36).[191]



(83)

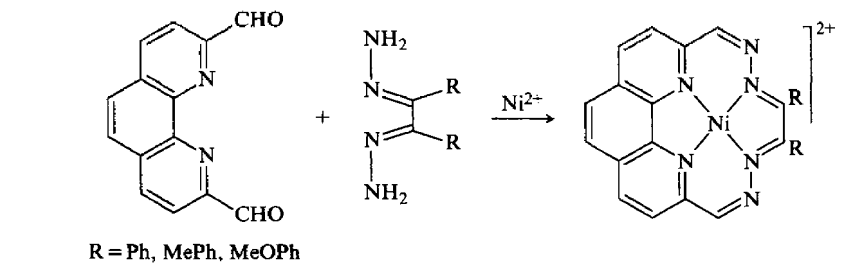
Scheme 36

The reaction of 2,6-diacetylpyridine with hydrazine in the presence of iron(II) salts yields a macrocyclic azine complex (equation 34).[192] Similar complexes of cobalt(II), zinc(II), magnesium(II) and scandium(III) have been prepared more recently.[193]



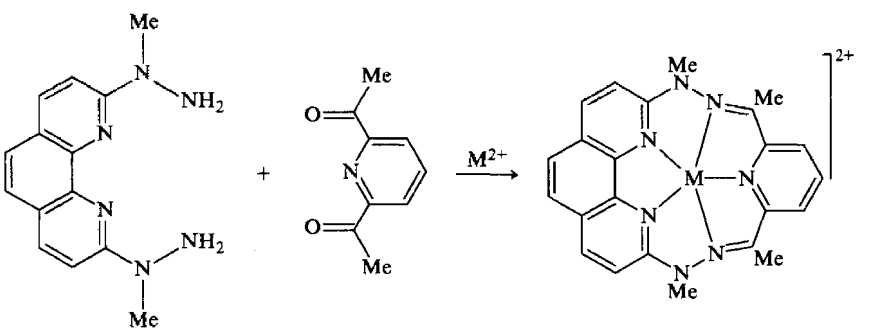
(34)

1,2-Dihydrazones undergo a template reaction with diformylphenanthroline to give highly-conjugated macrocyclic complexes (equation 35).[194] The reverse combination of reagents has also been found to yield macrocyclic complexes but in this case they are quinquedentate. The dicarbonyl compound was 2,6-diacetylpyridine and a dihydrazinophenanthroline was the other reagent, while the templating metals were zinc(II), cadmium(II), manganese(II) and iron(II) (equation 36).[194,195] The zinc(II) complex has been reduced with sodium borohydride to give a complex of the more flexible macrocyclic ligand (**88**).[196]

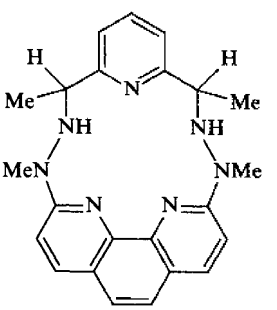


R = Ph, MePh, MeOPh

(35)

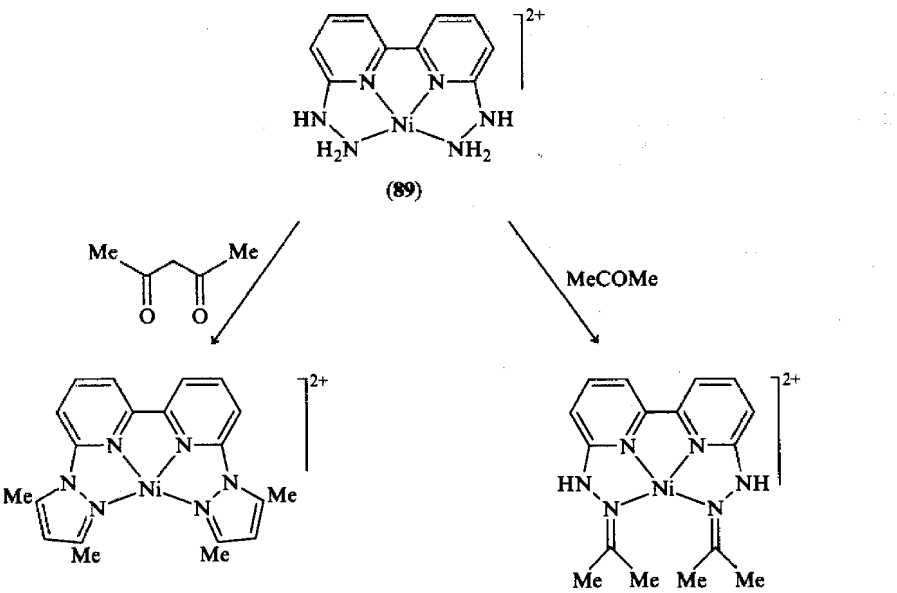


(36)

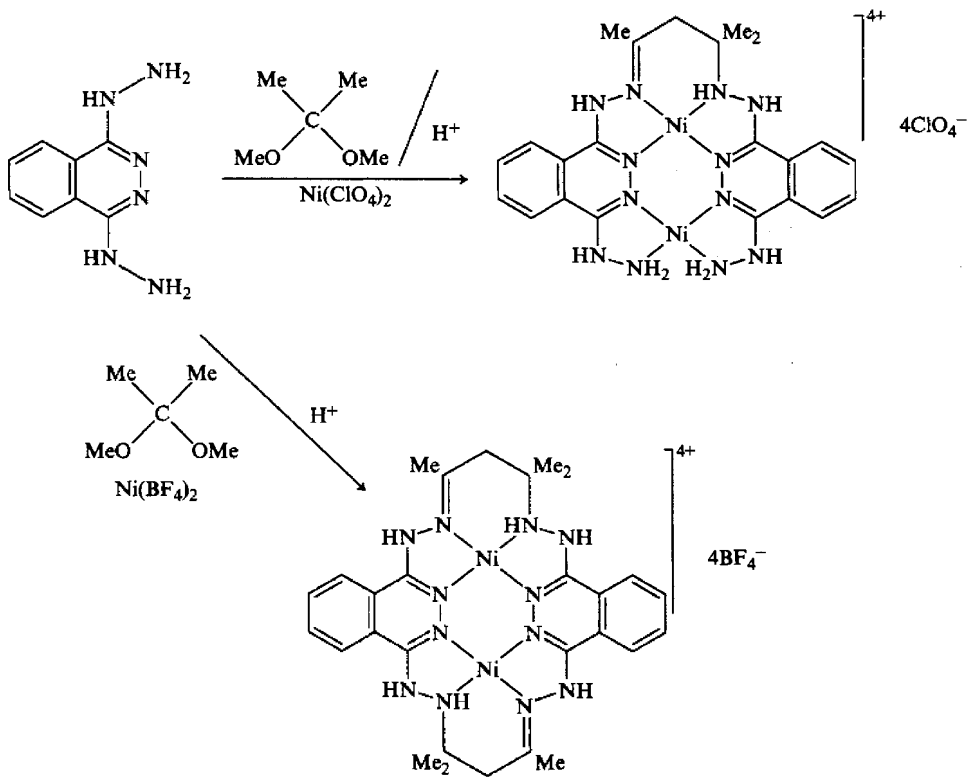


(**88**)

The reaction of the nickel(II) perchlorate complex (**89**) with acetone and related ketones yields simple hydrazone complexes rather than macrocyclic complexes resulting from a Curtis-type reaction. Acetylacetone also fails to bridge the bis(hydrazine) and instead yields a pyrazole derivative (Scheme 37).[197,198] In contrast to this result, 1,4-dihydrazinophthalazine undergoes a template reaction with 2,2-dimethoxypropane, a source of acetone, in the presence of nickel(II) fluoroborate and a trace of fluoroboric acid (Scheme 38).[199]



Scheme 37

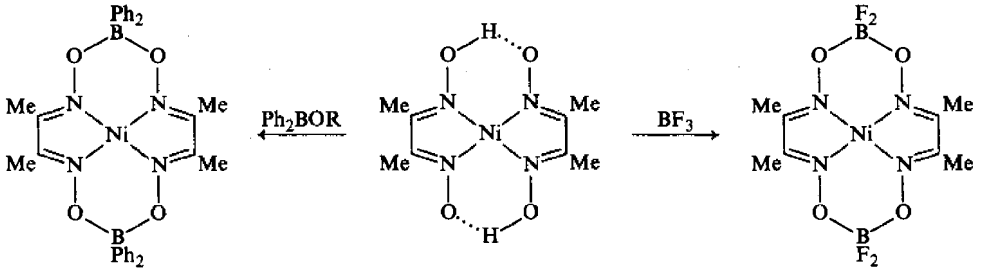


Scheme 38

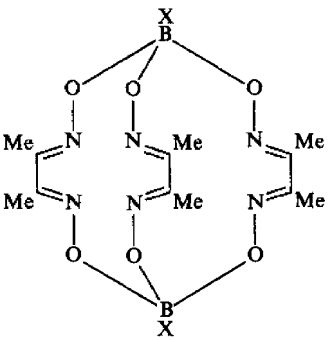
61.1.2.6 Oximes

Formation of oxime complexes under thermodynamic template conditions does not appear to have been recorded, presumably because oximes themselves are easy to prepare and isolate and are fairly resistant to hydrolysis. Oxime complexes coordinated at nitrogen are, however, capable of undergoing kinetic template reactions at oxygen. Treatment of bis(dimethylglyoximato)-nickel(II) with boron trifluoride etherate gave a very stable macrocyclic complex[200] and a related complex was produced from a diphenylborinic acid ester (Scheme 39).[201] Similar reactions occur to give complexes of iron(II), copper(II) and palladium(II). On the other hand, cobalt(III) and iron(II) complexes of clathrochelate ligands (**90**) incorporating three dimethylglyoxime moieties can be prepared from oxime complexes, or the combination of the oxime ligand and metal salt,

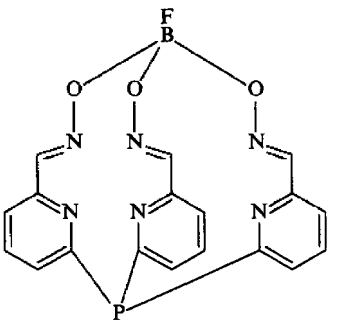
in reaction with a wide variety of boron reagents.[202–204] Other Lewis acids such as tin(IV) chloride and tetrachlorosilane can be used for similar capping reactions.[203] Kinetic template reactions also lead to clathrochelate complexes of the ligand (**91**), by combination of tris(2-aldoximo-6-pyridyl)phosphine with iron(II), cobalt(II), nickel(II) or zinc(II) fluoroborates and distillation with boron trifluoride.[205–207] Both cage types (**90**) and (**91**) promote trigonal prismatic geometry in their complexes.



Scheme 39

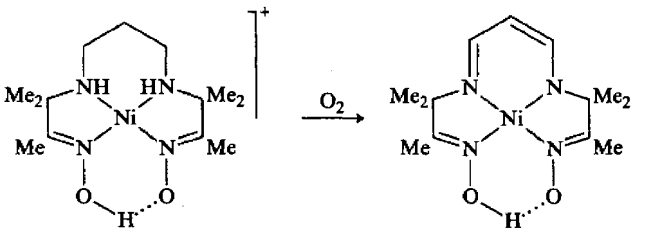


(**90**) X = F, OH, OR



(**91**)

Certain ligands containing oxime groups are susceptible to oxidative dehydrogenation reactions of the type already discussed. While the oxime groups are not at the site of the reaction, they contribute to the overall molecular geometry which seems to encourage such processes. An example of oxidative dehydrogenation in oxime complexes is shown in equation (37).[208]



(37)

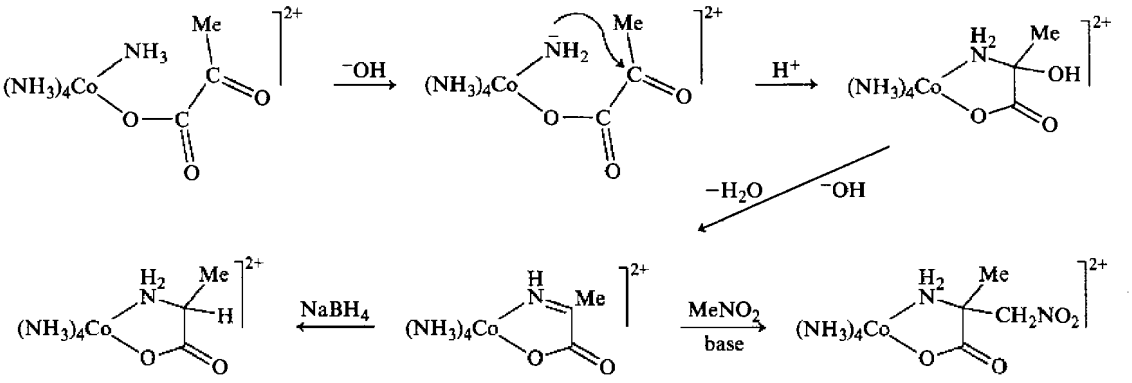
61.1.2.7 Imines Formed by Kinetic Template Reactions

Sargeson and his coworkers have developed an area of cobalt(III) coordination chemistry which has enabled the synthesis of complicated multidentate ligands directly around the metal. The basis for all of this chemistry is the high stability of cobalt(III) ammine complexes towards dissociation. Consequently, a coordinated ammonia molecule can be deprotonated with base to produce a coordinated amine anion (or amide anion) which functions as a powerful nucleophile. Such a species can attack carbonyl groups, either in intramolecular or intermolecular processes. Similar reactions can be performed by coordinated primary or secondary amines after deprotonation. The resulting imines coordinated to cobalt(III) show unusually high stability towards hydrolysis, but are reactive towards carbon nucleophiles. While the cobalt(III) ion produces some iminium character, it occupies the normal site of protonation and is attached to the nitrogen atom by a kinetically inert bond, and thus resists hydrolysis.

The formation and reactions of imines bound to cobalt(III) and related metal ions will be considered together in the following discussion, because both types of reactions are combined in synthetically useful sequences.

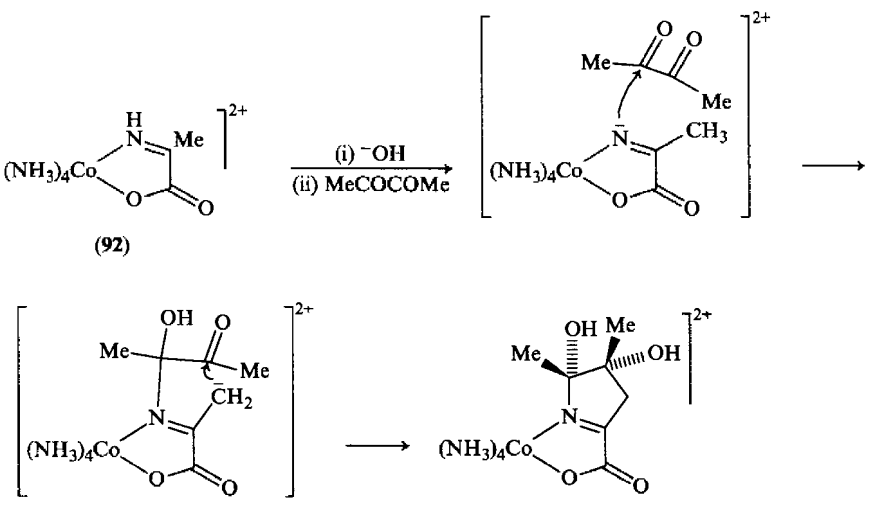
One of the earliest observations of imine formation on cobalt(III) was that arising from the treatment of pyruvatopentamminecobalt(III) with base to pH $\geqslant$ 12 to give the imine chelate (**92**)

(Scheme 40).[209,210] After the initial carbinolamine formation, further base treatment is required to deprotonate the bound amine and allow dehydration to occur. The imine chelate (**92**) undergoes attack by nucleophiles such as hydride ion and the anion of nitromethane (Scheme 40), and these reactions serve as a basis for more complex processes of synthetic utility. For instance, the addition of a molar equivalent of hydroxide ion to the imine chelate (**92**) followed by an excess of biacetyl led to the formation of a pyrroline ring on the chelate ligand (Scheme 41).[211] It is proposed that the nitrogen–carbon bond is formed initially, as proton exchange on the imine methyl is much more rapid when the nitrogen atom is alkylated. The hydroxyl groups in the product are *cis* and no evidence has been found for the presence of the *trans* isomer. Hydrogen bonding is suggested as a possible reason for the stereospecificity of the reaction.



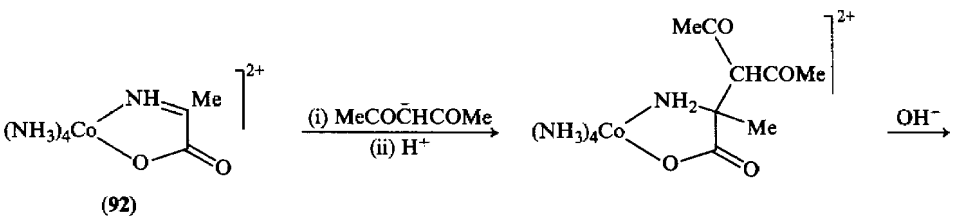
(92)

Scheme 40

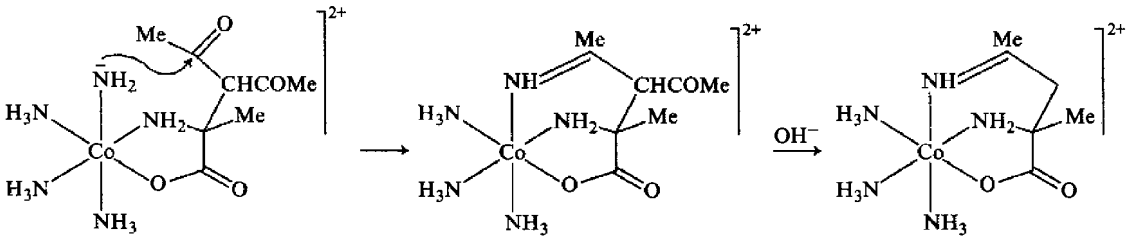


(92)

Scheme 41

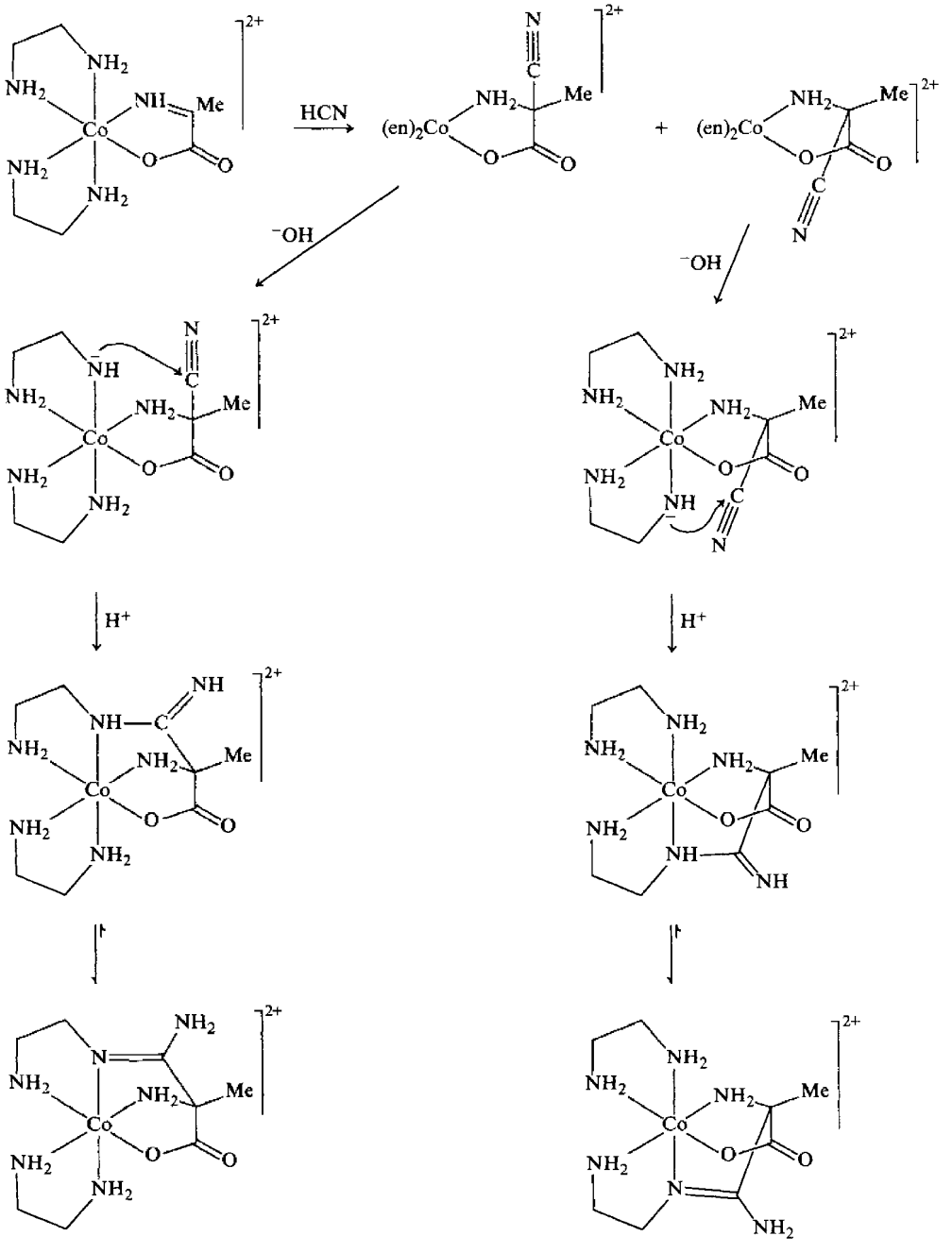


(92)



Scheme 42

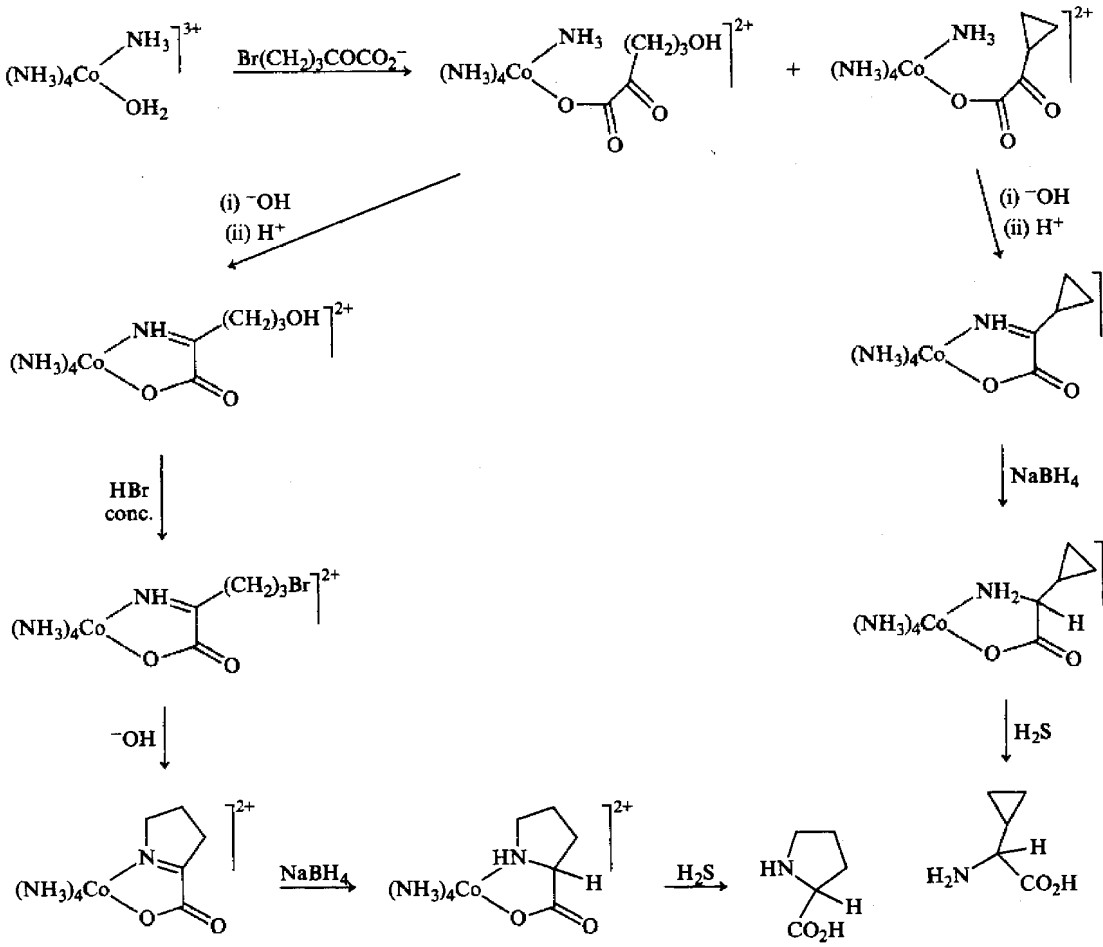
The acetylacetone carbanion undergoes addition to the imine carbon atom of complex (**92**) but subsequent cyclization and deacylation processes occur (Scheme 42).[212] The apical ammonia group is the most acidic and consequently is favoured to cyclize on to the carbonyl group. In the bis-(1,2-diaminoethane) complex related to the imine chelate (**92**), the two apical nitrogen atoms are no longer geometrically equivalent. Thus two products are formed when hydrogen cyanide is added to the complex and subsequent cyclization takes place (Scheme 43).[213] However, the cyclization reaction is stereoselective.



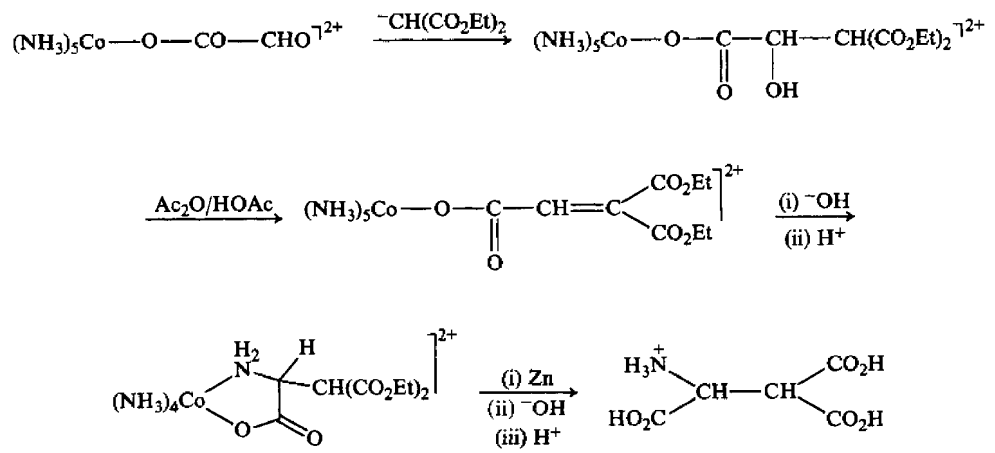
Scheme 43

Hydride reduction of imine chelates such as (**92**) offers a synthetic route to α-amino acids, as demonstrated for cyclopropyl glycine and proline (Scheme 44).[214]

A related reaction sequence that involves the Michael addition of a coordinated amide ion to an α,β-unsaturated malonate results in the formation of a β-carboxyaspartic acid complex. The acid is isolated as the calcium salt by reduction of cobalt(III) followed by recovery and hydrolysis of the diethyl ester (Scheme 45).[215]

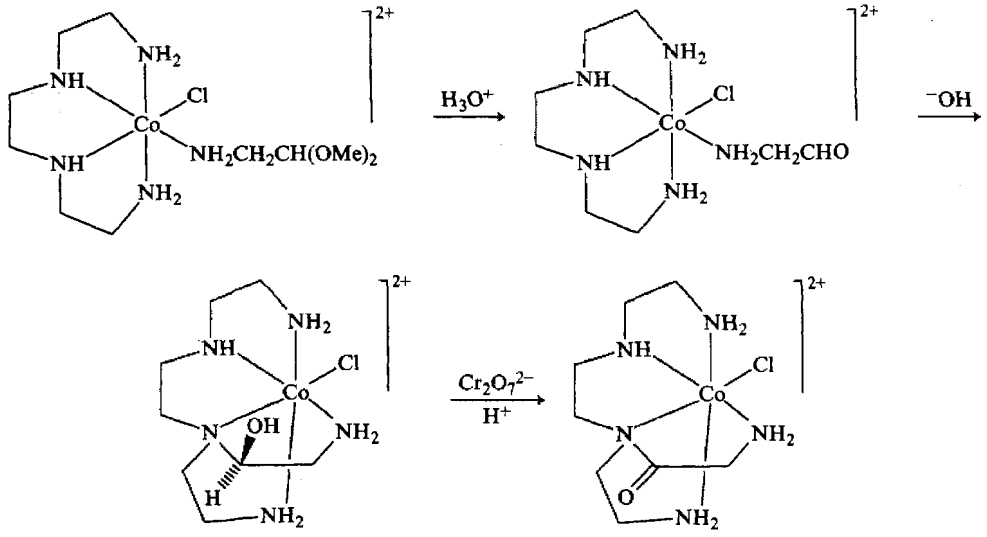


Scheme 44

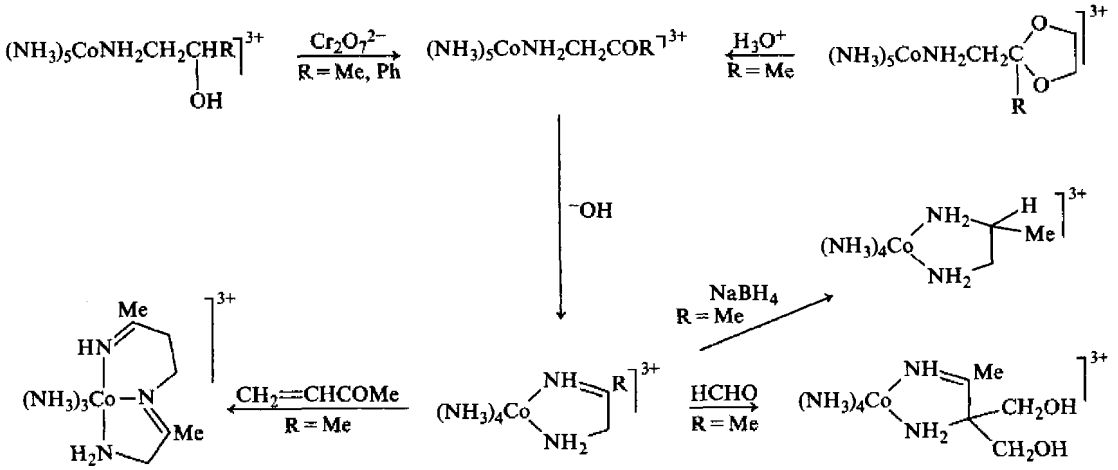


Scheme 45

Coordinated amide ions have also been induced to undergo intramolecular imine formation with the carbonyl groups of amino aldehydes and ketones. Such compounds are highly reactive and it is convenient in most cases to generate them bound to cobalt(III) by the amino group, which is thus protected. For example, aminoacetaldehyde can be coordinated to cobalt(III) and because of the inertness of the cobalt–nitrogen bond, the acetal group can be hydrolyzed by acid to liberate the reactive aldehyde. Reaction in the case of a triethylenetetramine complex stops at the carbinolamine stage (Scheme 46).[216,217] This complex can, however, be oxidized with dichromate to give an α-amino amide chelate ring. The ring-closure reaction is stereospecific as shown, presumably because the direction of approach of the successful nucleophile to the carbonyl group is optimal. Aminoacetophenone and aminoacetone can be formed on cobalt(III) by oxidation of the



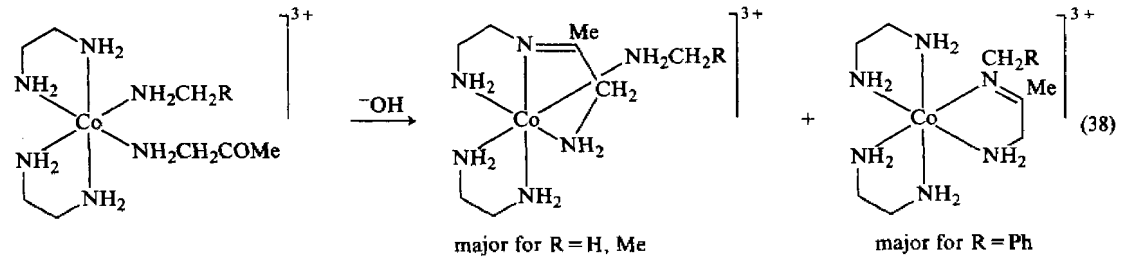
Scheme 46



Scheme 47

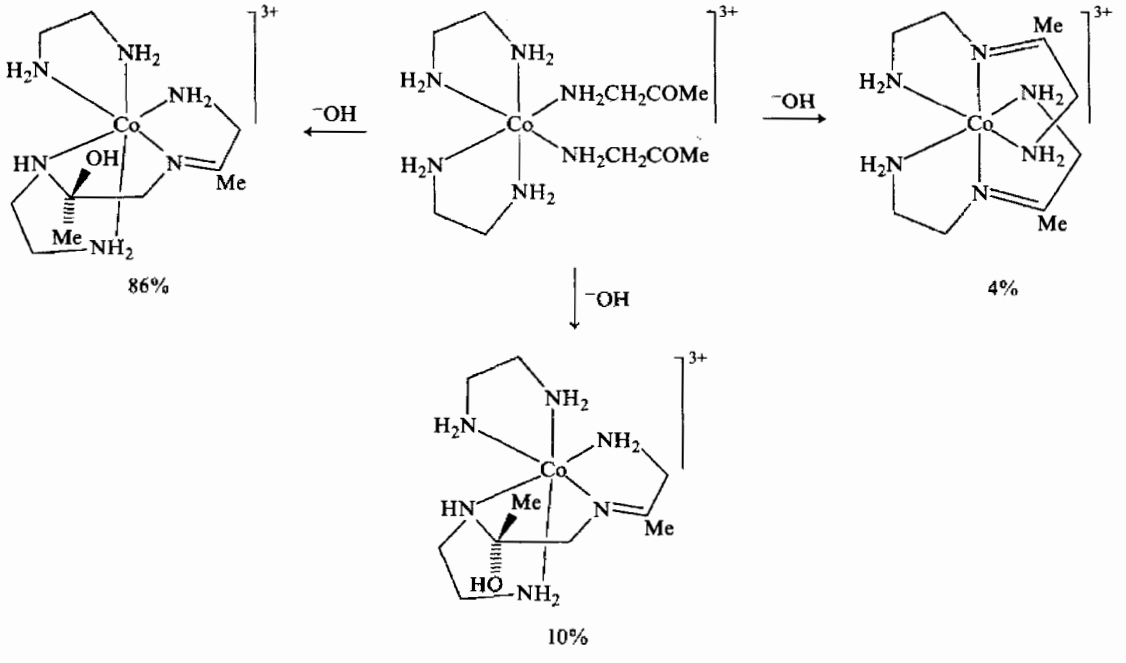
related alcohols or by hydrolysis of a dioxolane. The resulting imine complex from aminoacetone has been investigated with respect to its reduction and also its carbanionic behaviour (Scheme 47).[217] Hydride reduction allows the formation of a substituted 1,2-diaminoethane ring, while methyl vinyl ketone extends the bidentate ring to a tridentate. Further extension of this latter process to the formation of a macrocyclic quadridentate ligand has not yet been achieved.

Cyclization of coordinated primary amines on to coordinated aminoacetone has also been investigated in bis(1,2-diaminoethane)cobalt(III) complexes, and the results show selectivity with respect to attack of the monoamine or 1,2-diaminoethane (equation 38).[218] A similar complex with two coordinated aminoacetone molecules undergoes the same type of stereoselective kinetic template reactions and yields complexes primarily of a new quadridentate ligand (Scheme 48).[219]

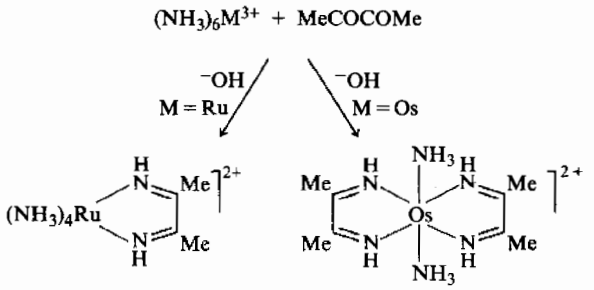


major for R = H, Me major for R = Ph (38)

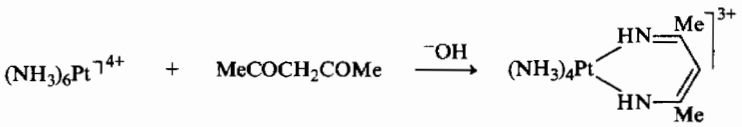
In similar but more complicated processes, chelated α-diimines can be formed by reaction of ruthenium(III) and osmium(III) ammine complexes with biacetyl; however, reduction of the metal also occurs (Scheme 49).[220] A β-diimine complex is obtained when acetylacetone undergoes reaction with hexaammineplatinum(IV) ions in basic solution (equation 39).[220]



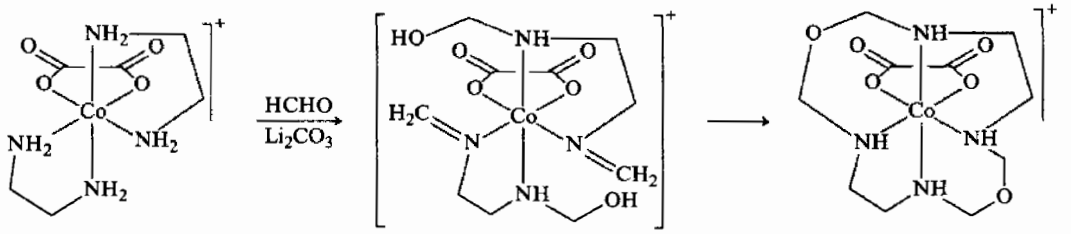
Scheme 48



Scheme 49



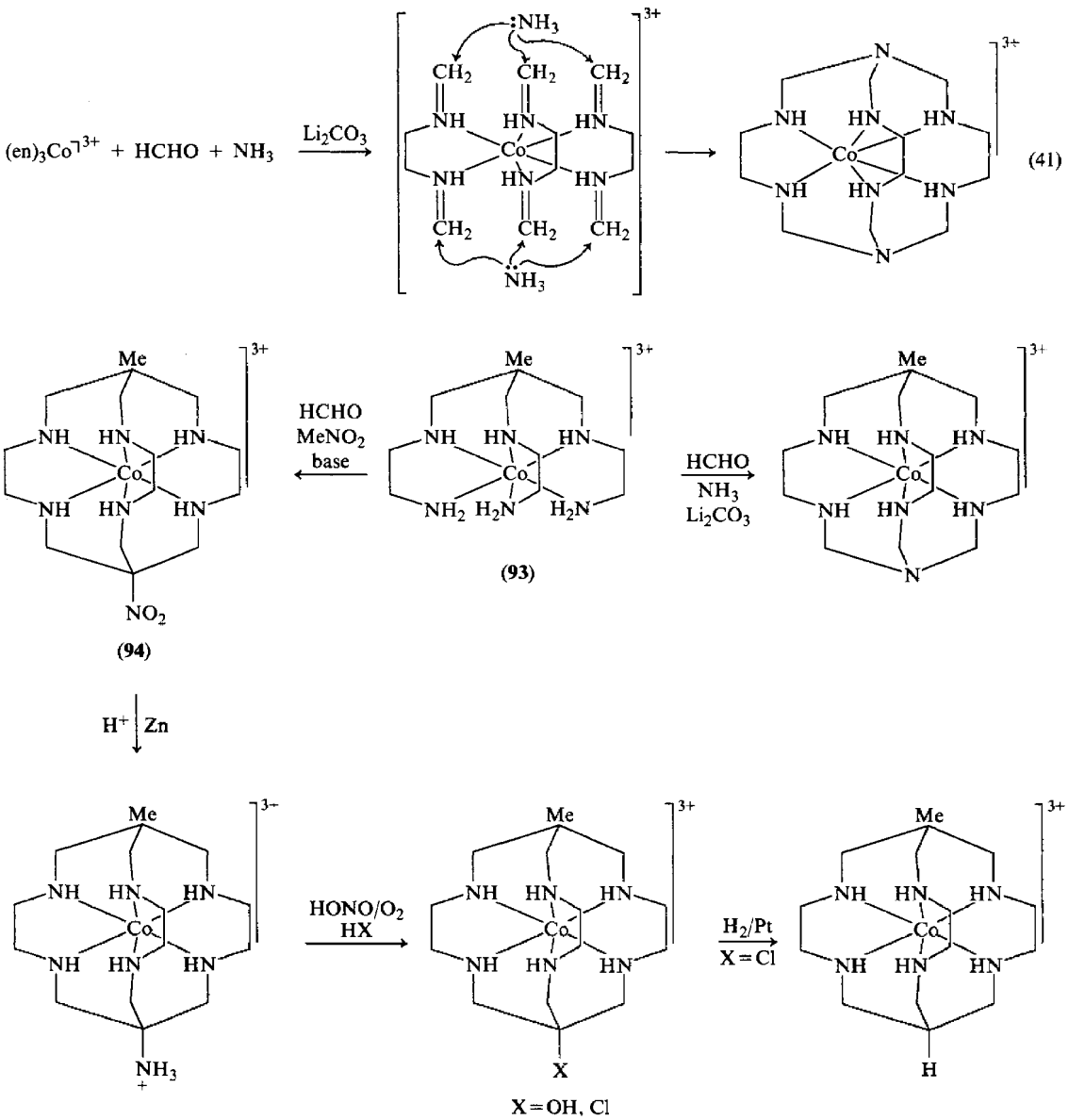
(39)



(40)

Conceptually the simplest reaction of a nucleophilic coordinated amide ion with a carbonyl compound would be that with formaldehyde. However, because of the high reactivity of formaldehyde such reactions are difficult to control and numerous pathways can lead to numerous products. Sargeson and coworkers discovered that the cobalt(III) ion can indeed control these reactions to build up useful multidentate ligands. Initially, in an attempt to react formaldehyde with a coordinated glycine, they accidentally found that formaldehyde also reacted with coordinated 1,2-diaminoethane to yield a macrocyclic ligand. The glycine ligand could be replaced by oxalate and macrocycle formation still occurred (equation 40).[221] In the extension of such a reaction to tris(1,2-diaminoethane)cobalt(III) a divalent oxygen atom cannot serve as a cap, so trivalent nitrogen and quadrivalent carbon were required. Thus, tris(1,2-diaminoethane)cobalt(III) ions, ammonia and formaldehyde combined in basic solution to yield an encapsulated cobalt(III) ion in a so-called 'sepulchrate' complex (equation 41).[222,223] The reaction must proceed in a stepwise

fashion *via* coordinated imines, but is only notionally represented in equation (41). The capping process is a new example of the Mannich reaction and has been extended to include the carbanion derived from nitromethane, but, surprisingly, not a methyl ketone carbanion such as that derived from acetophenone. The amine ligands can also be varied to include a precapped sexadentate (**93**) (Scheme 50).[224,225] The resultant encapsulated complex (**94**) can be further manipulated by transformation of the nitro group to amino, hydroxy, chloro and a proton (Scheme 50). In addition to cobalt(III), these encapsulation reactions can be carried out on complexes of rhodium(III) and iridium(III),[226] chromium(III)[224] and platinum(IV),[227] with a high degree of stereospecificity.

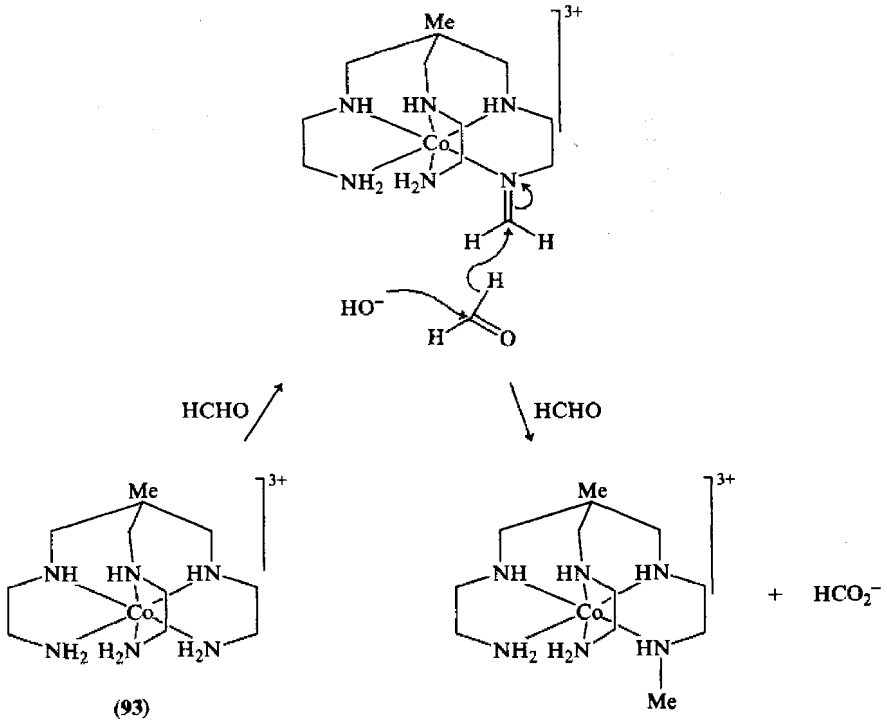


Scheme 50

In addition to encapsulation, the complex (**93**) also undergoes methylation, presumably by reduction of the carbinolamine formed from condensation of formaldehyde and (**93**) in a Canizzaro-type reaction (Scheme 51).[223]

The template encapsulation has recently been extended still further to the cobalt(III) complex of the vicinal tridentate 1,1,1-tris(aminomethyl)ethane but leads to a surprising set of products, which in retrospect shows the geometrical influence of the original tridentate ligand (Scheme 52).[228] Although mixtures of products are formed in rather modest yields, the individual compounds can be separated by chromatography.

Many interesting properties are exhibited by the encapsulated metal ions, but discussion of these is outside the scope of this chapter.



(93)

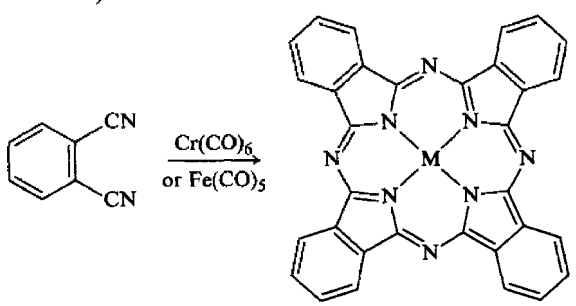
Scheme 51

61.1.3 SYNTHESIS AND SOME REACTIONS OF PHTHALOCYANINE, PORPHINOID AND CORRINOID MACROCYCLES

61.1.3.1 Phthalocyanines and Related Compounds

One of the first examples of metal ions facilitating macrocycle formation was the synthesis of metal phthalocyanines (**95**) from 1,2-dicyanobenzene or 2-cyanobenzamide (Scheme 53).[229–231] This example of macrocycle synthesis has been applied to a very wide range of metal salts of various valencies, and is of great commercial interest. As this area of chemistry has been reviewed frequently and is dealt with in Chapter 21.1, only a brief consideration of the most important template reactions will be presented here.

Convenient synthesis of chromium and iron phthalocyanines can be achieved by reaction of 1,2-dicyanobenzene with chromium hexacarbonyl or iron pentacarbonyl respectively in refluxing chloronaphthalene (equation 42).[232]

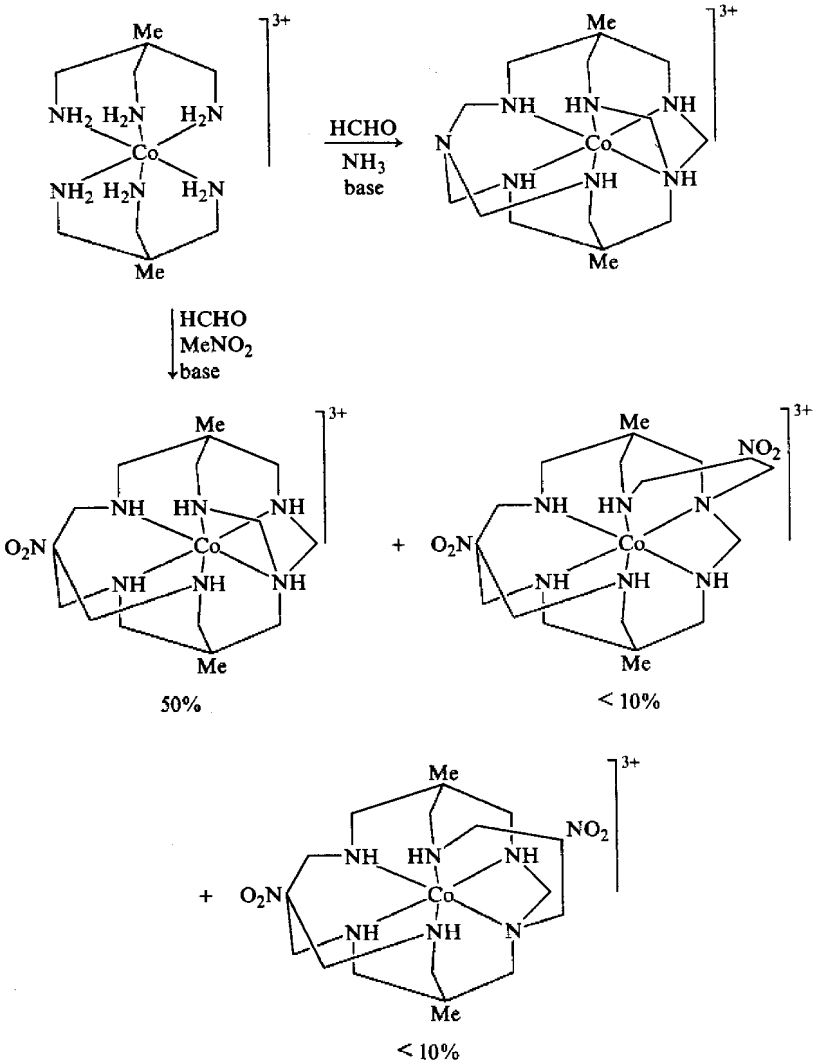


(42)

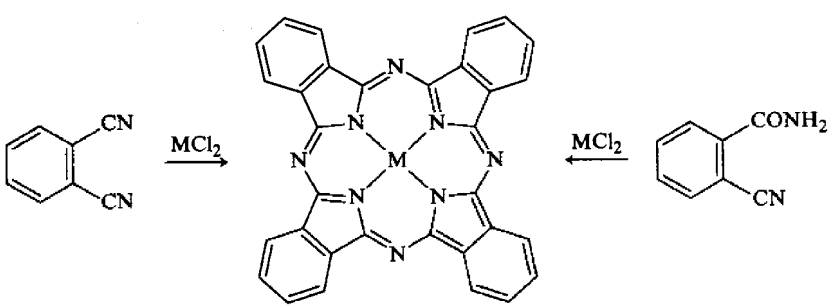
(**95**) M = Cr or Fe

Although the precise mechanism of formation of phthalocyanines is unknown, it is generally thought that isoindoline intermediates are involved. A notional cyclization process could be that shown in equation (43).[233] Template synthesis of phthalocyanines can also be achieved starting with 1,3-diiminoisoindoline and various analogs can be obtained from combinations of starting materials.[234] Ligands such as (**96**) and (**97**) can be synthesized in this manner.[235,236]

Template reactions of 1,2-dicyanobenzenes with uranyl salts lead to the synthesis of superphthalocyanines (Scheme 54).[237,238] The uranyl ion can be displaced from the macrocycle by a range of metal salts, but a ring contraction occurs to yield normal phthalocyanine complexes (Scheme 54).[238,239]

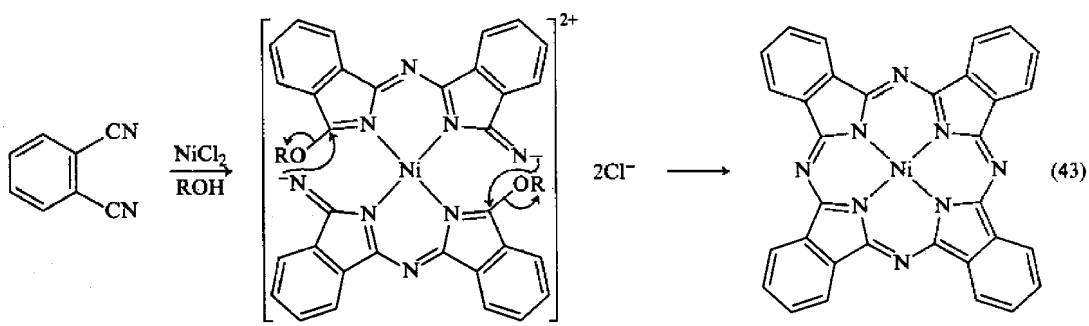


Scheme 52

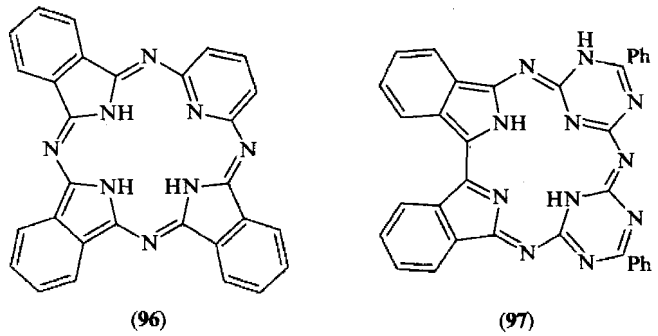


(95)

Scheme 53

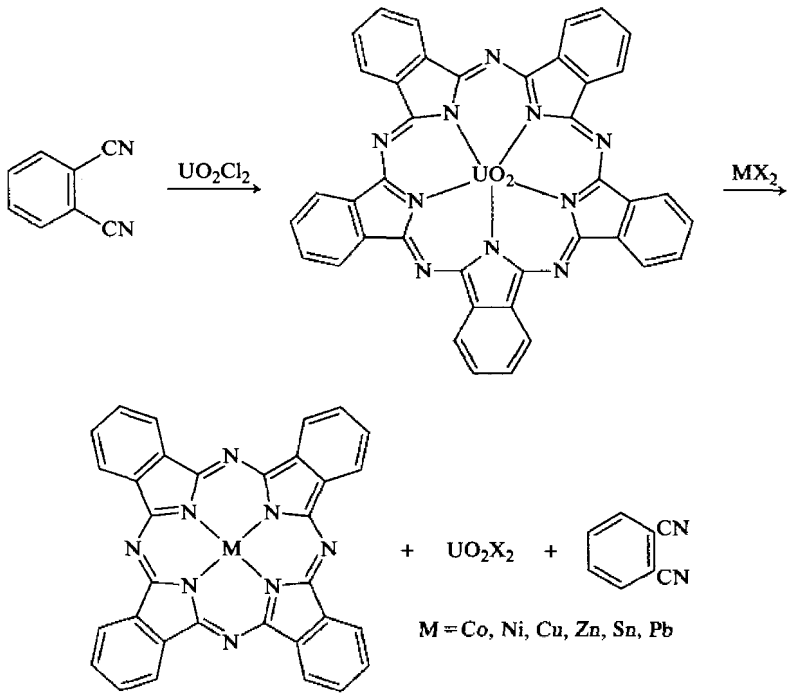


(43)



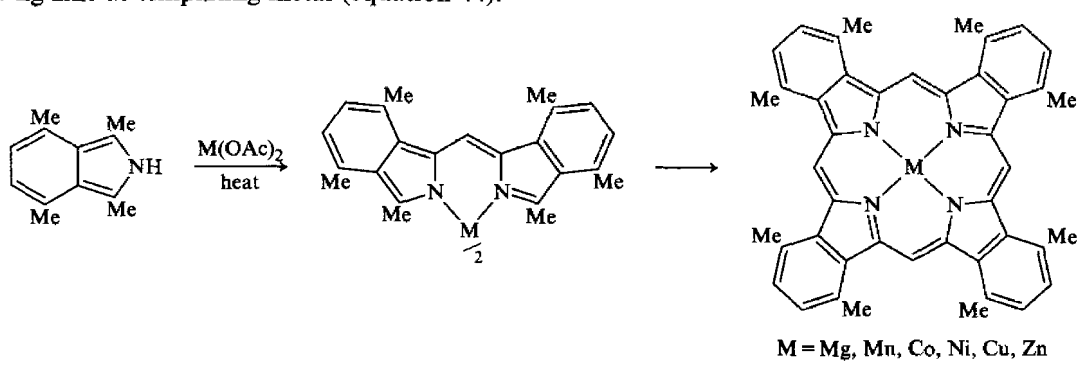
(96)

(97)



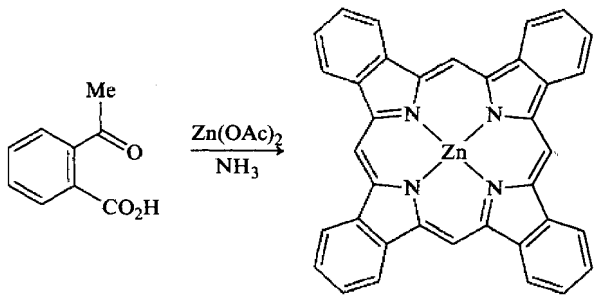
Scheme 54

Several syntheses of tetrabenzoporphyrin complexes make use of similar template strategies to those used in phthalocyanine synthesis, so they will be discussed here. An isoindole has been found to undergo a very complex series of reactions promoted by a range of metal ions in refluxing 1,2,4-trichlorobenzene to produce tetrabenzoporphyrin complexes (Scheme 55).[240] In contrast, an extremely simple synthesis of tetrabenzoporphyrin can be achieved from 2-acetylbenzoic acid, using zinc as templating metal (equation 44).[241]

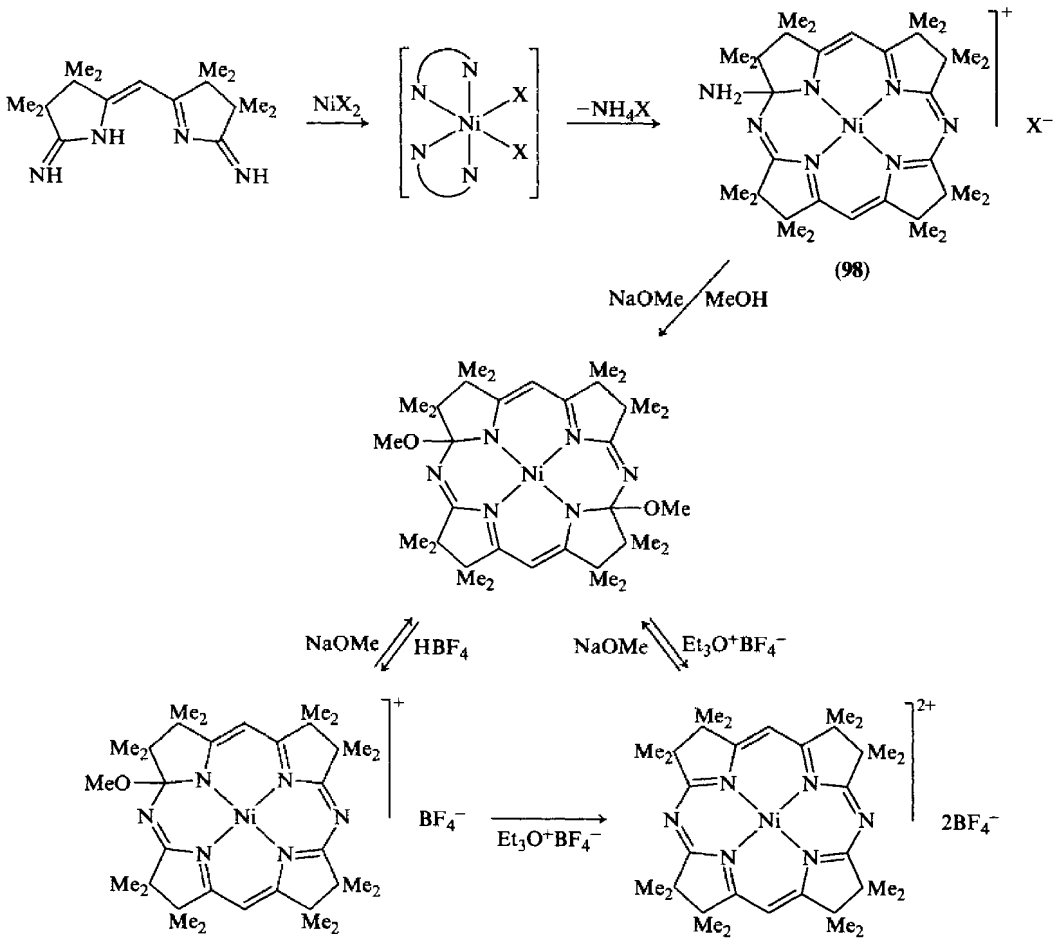


Scheme 55

The formation of the macrocyclic complex (**98**) is a template reaction reminiscent of phthalocyanine synthesis, and aza linkages are formed (Scheme 56).[242] The resulting complex (**98**) can be transformed into a complex with a fully conjugated macrocyclic ligand. The dibromocobalt(III) complex related to (**98**) can also be prepared and can function to some extent as a model for vitamin B_{12}.[243]

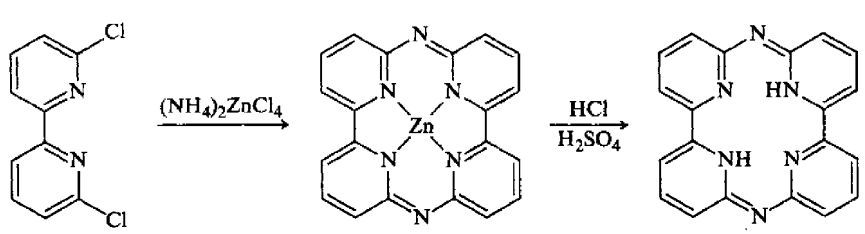


(44)



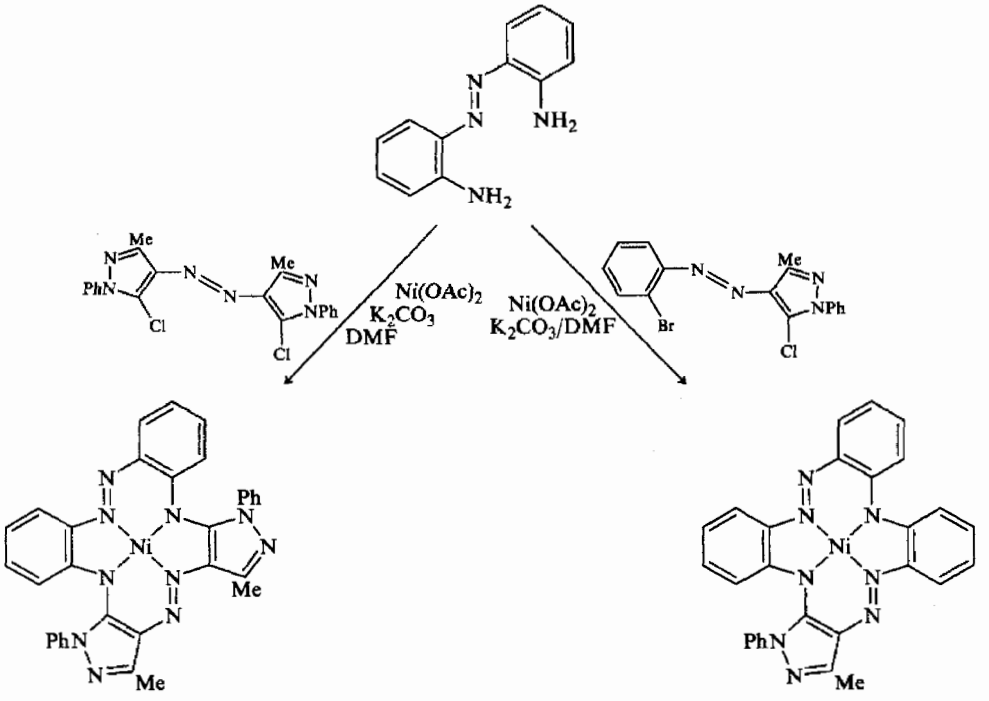
Scheme 56

Two further miscellaneous classes of macrocyclic metal complexes are included in this section because they have structural features such as aza linkages and a high degree of unsaturation associated with fused aromatic rings. Ogawa and coworkers have shown that when 2,4-dichloro-1,10-phenanthroline is fused with ammonium tetrachlorozincate, a macrocyclic zinc complex is produced. The metal can be removed subsequently by acidic treatment (Scheme 57).[244] The free macrocycle can also be prepared by non-template methods, which however do not appear to be as effective as they require reaction of the dichlorophenanthroline with 2,9-diaminophenanthroline.[245]

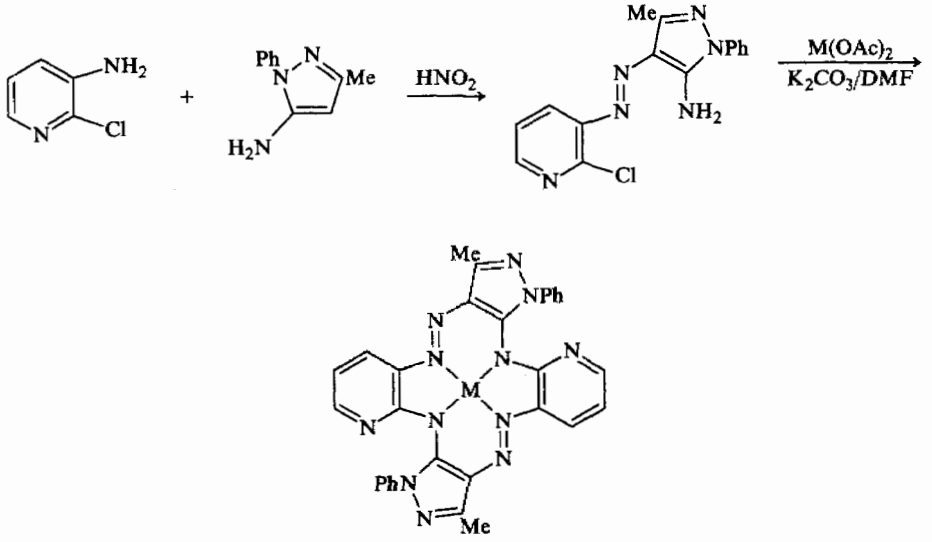


Scheme 57

An extensive series of neutral macrocyclic complexes, mainly of nickel(II), copper(II), platinum(II) and palladium(II), has been developed by Dziomko and coworkers. The cyclization step in the template reaction is a nucleophilic aromatic substitution of an arylamine on to a haloaryl azo compound. A variety of aryl and heteroaryl rings can be incorporated in different combinations. For instance, a diaminoazo compound can be combined with a dihaloazo compound (Scheme 58).[246,247] Another synthetic strategy involves the dimerization of an aminohaloazo compound and leads to more symmetrical macrocyclic complexes (Scheme 59).[248,249] Most recently, dihalodiazo compounds have been synthesized from dihydrazines and pyrazolinediones and undergo template reactions with simple 1,2-diamines (Scheme 60).[249,250]



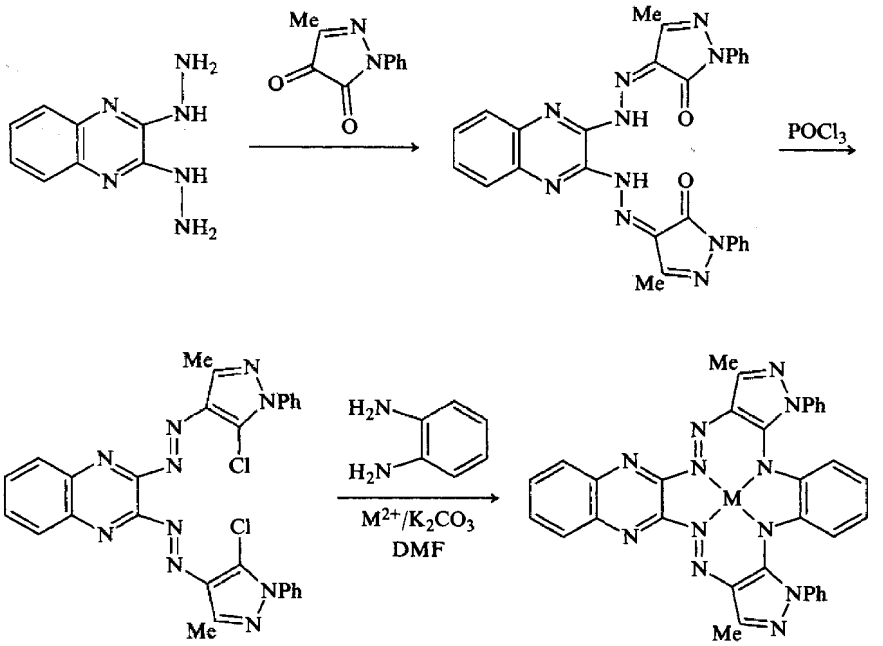
Scheme 58



Scheme 59

61.1.3.2 Porphinoid and Corrinoid Compounds

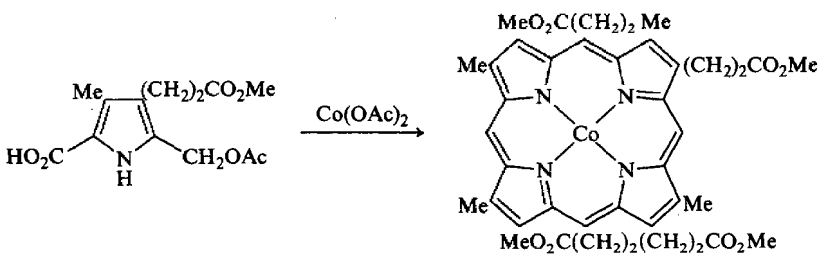
The synthesis of porphyrins in many cases depends upon reactions, especially cyclizations, of ligands coordinated to suitable metals. In this section, only this aspect will be considered. The enormous array of organic reactions carried out on porphyrin complexes is not appropriate for



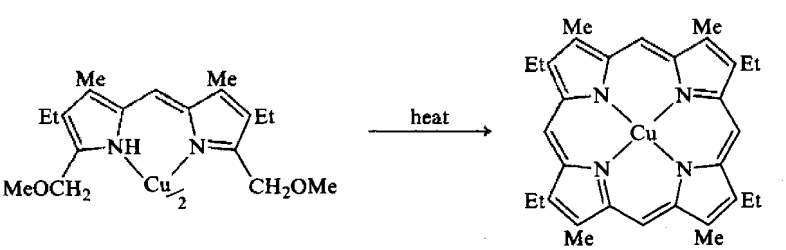
Scheme 60

discussion here as the reactions usually are not influenced significantly by the metal ion present, and furthermore porphyrin chemistry is considered separately in Chapter 21.1.

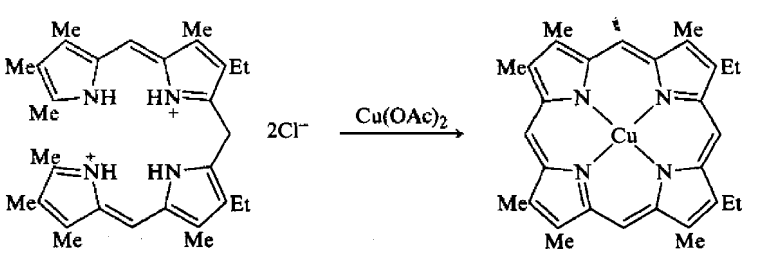
Porphyrin synthesis can be enhanced by metal template methods using several strategies, including tetramerization of pyrrole derivatives (equation 45),[251] dimerization of dipyrrolomethenes (equation 46)[252] and cyclization of 1,19-dideoxybiladiene-*ac* derivatives (equation 47).[252] These derivatives can also be induced to undergo direct base-catalyzed template cyclization to octadehydrocorrins of different chromophores depending on the 1,19-substituents (Scheme 61).[253–255] The cationic complex (**99**) can be transformed by thermal ring expansion processes to porphyrin derivatives (Scheme 62).[253]



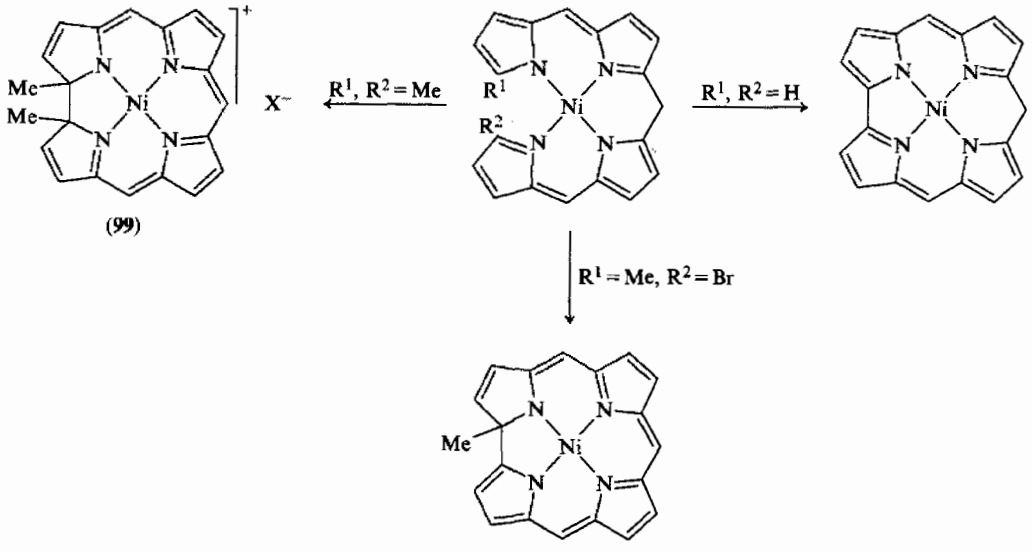
(45)



(46)

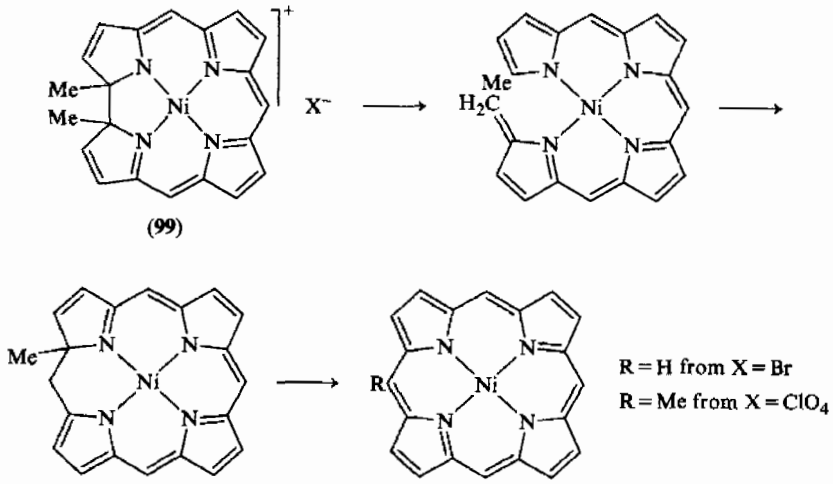


(47)



(99)

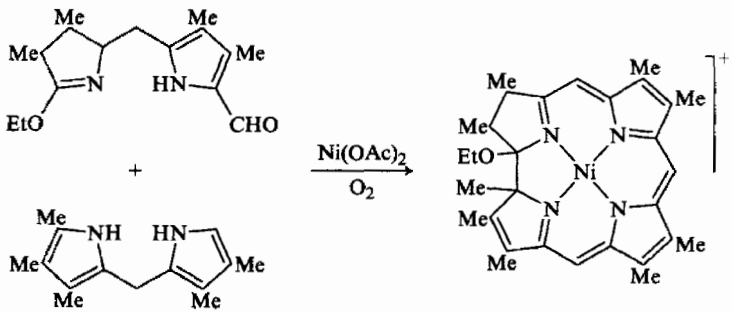
Scheme 61



(99)

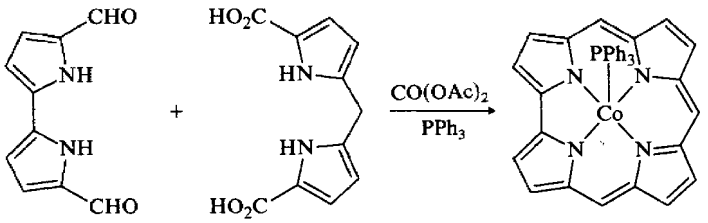
Scheme 62

Dehydrocorrin complexes can also be prepared in [2 + 2]-type template syntheses as shown in equations (48)[256] and (49).[257] The cyclization technique involving imino esters (see equation 48) has been used to great effect by Inhoffen's group in the template preparation of dehydrocorrins from biladiene derivatives (equation 50).[258,259] Very recently, direct cyclization of a cyanotetrapyrroloid complex has yielded a hexadehydrocorrin, after a sequence involving base-induced elimination of cyanide ion and protonation (Scheme 63).[260]

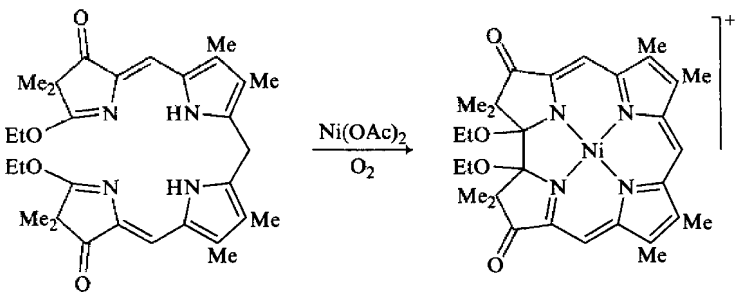


(48)

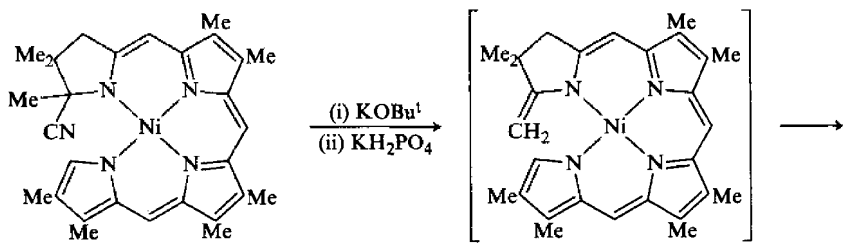
Some of the earliest attempts to prepare dehydrocorrin derivatives used a tetrapyrrole compound already containing a direct linkage between the two central rings. When its palladium(II) derivative was treated with formaldehyde and hydrochloric acid it underwent cyclization but with the insertion of an oxygen atom rather than the desired carbon bridge (equation 51).[261] Subsequent treatment of the same starting material with ammonia, methylamine or sodium sulfide gave rise to related macrocyclic products.

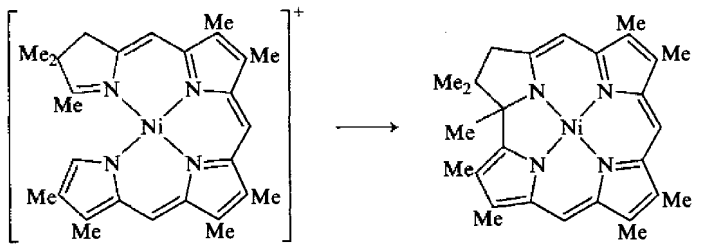


(49)

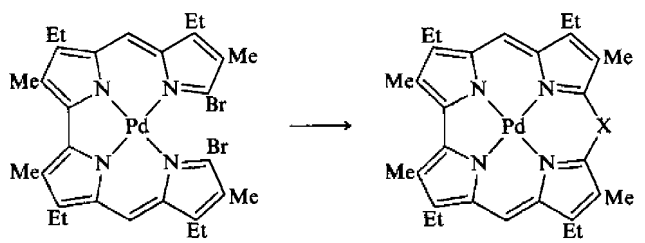


(50)



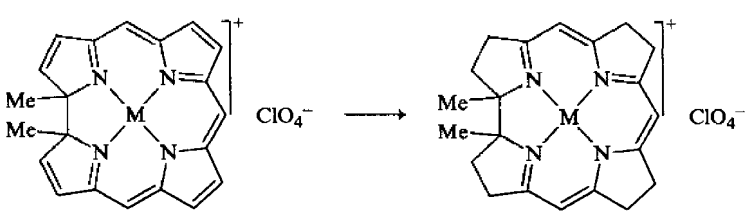


Scheme 63



(51)

The underlying reason for the investigation of dehydrocorrins by the synthetic techniques of pyrrole and porphyrin chemistry was that subsequent hydrogenation might lead to the corrin nucleus of vitamin B_{12}. This objective was achieved by Johnson's group with the selective hydrogenation of the β-double bonds of the complex (**99**) (equation 52).[262]

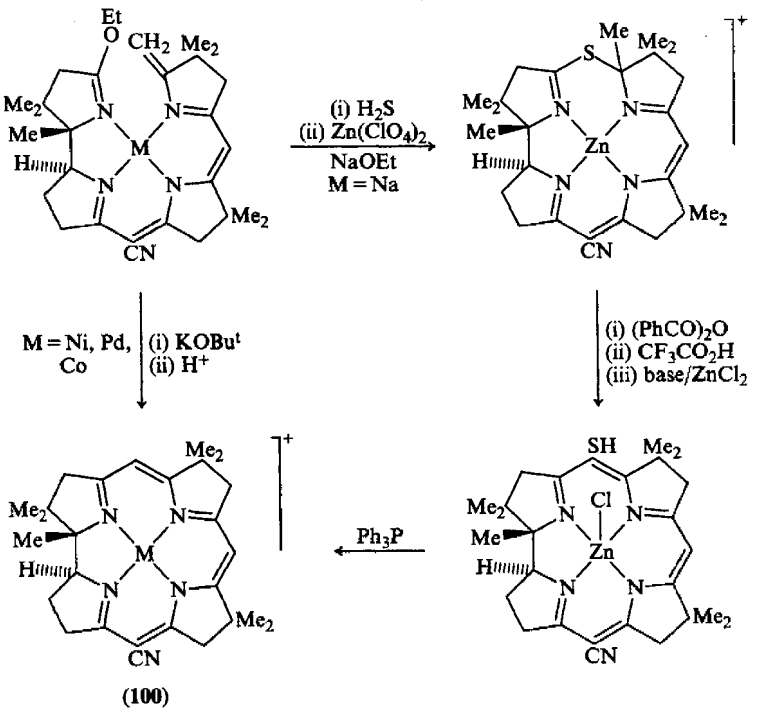


(**99**) M = Ni, Co

(52)

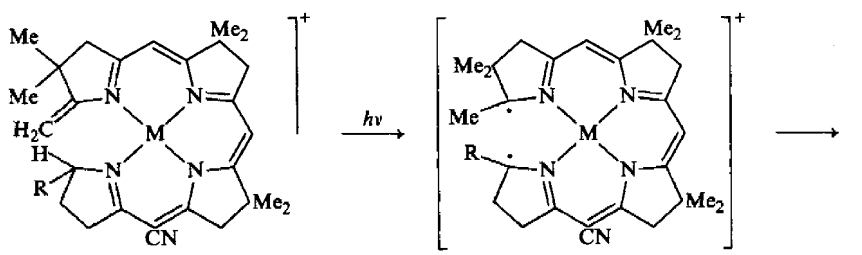
More direct attempts by Eschenmoser and his group to build up corrins at the desired oxidation level have unearthed a wealth of kinetic template cyclization processes. These have in turn developed into techniques which can now be applied to porphinoid compounds as well. A brief summary of the types of template cyclization reactions is relevant here.

Initial cyclizations were effected by the addition of an enamine to an imidate ester, both groups being suitably located by ligand coordination.[263] An analogous process can be carried out on a thioimidate but a sulfide is formed and removal of sulfur with consequent ring contraction yields the corrin (**100**).[264] These two complementary routes can be effected with different metal ions, nickel(II), palladium(II) and cobalt(III) in the first route, zinc(II) in the second. Removal of zinc ions easily provides the free corrin macrocycle. These two routes are summarized in Scheme 64. The sulfide contraction route was used in the Eschenmoser–Woodward total synthesis of vitamin B_{12}.[265]

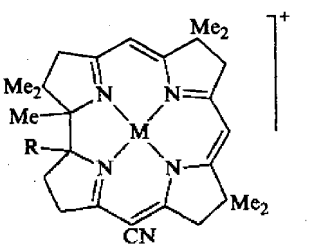


(**100**)

Scheme 64



(**101**) R = H
(**102**) R = CO_2H

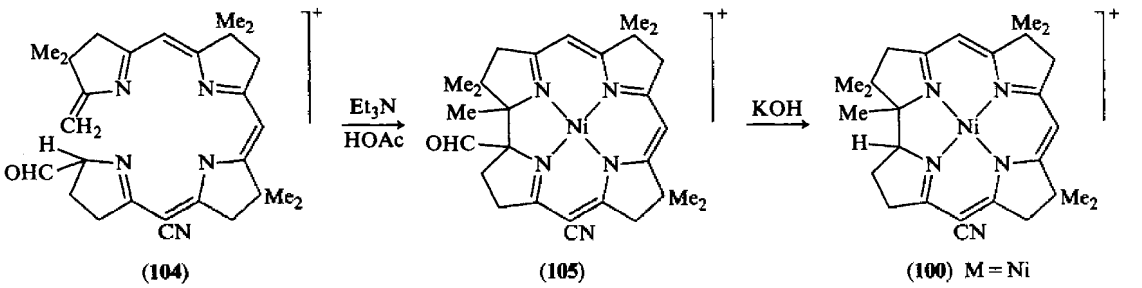


(**100**) R = H
(**103**) R = CO_2H

Scheme 65

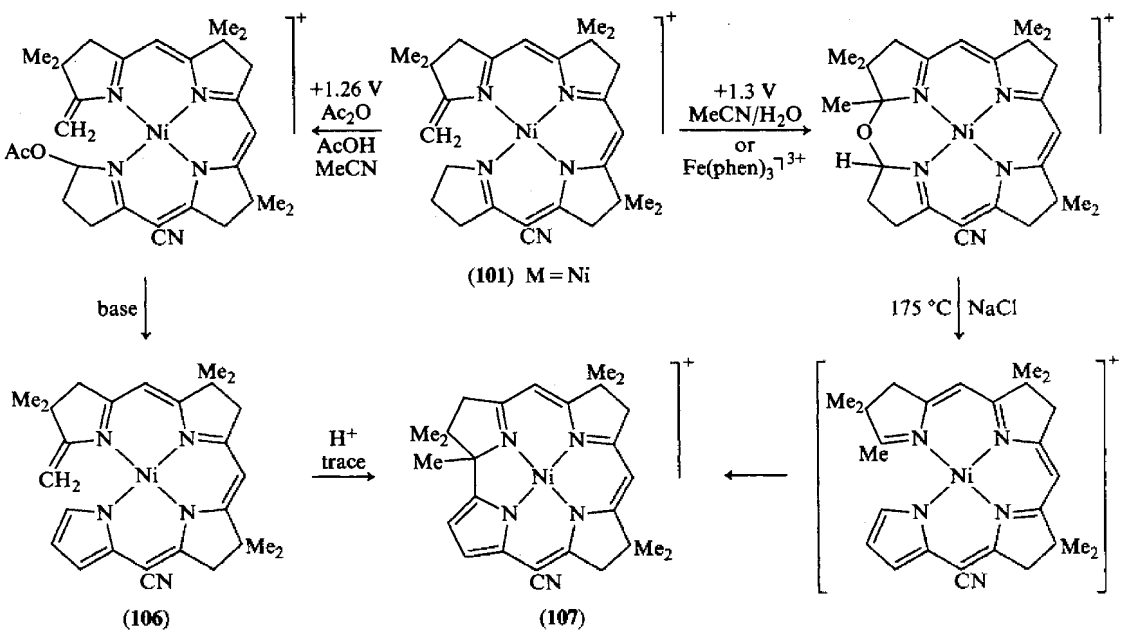
A further route to the corrins (**100**) was found to be the photocyclization of secocorrinoid complexes (**101**), involving an antarafacial sigmatropic 1,16-hydrogen transfer to give a formal diradical intermediate which undergoes antarafacial 1,15-($\pi-\sigma$) isomerization (Scheme 65).[266] This route has been applied to the Eschenmoser total synthesis of vitamin B_{12}.[265] The photocyclization is dependent on the nature of the central metal ion, proceeding most successfully with lithium, magnesium, zinc or cadmium, slowly with platinum and palladium but not at all with nickel, copper or cobalt.[267]

The cadmium secocorrinoid carboxylic acid (**102**; M = Cd) also undergoes photocyclization to the acid (**103**; M = Cd), which on transmetallation to the nickel(II) complex (**103**; M = Ni) and treatment with triethylamine and acetic acid yields the parent corrin complex (**100**; M = Ni).[268] The decarboxylation process is extremely facile. A related base-catalyzed cyclization of the secocorrinoid aldehyde (**104**) gives the corrin complex (**105**), which can be decarbonylated to the parent complex (**100**; M = Ni) by treatment with potassium hydroxide (Scheme 66).[268]



(**104**) (**105**) (**100**) M = Ni

Scheme 66



(**101**) M = Ni

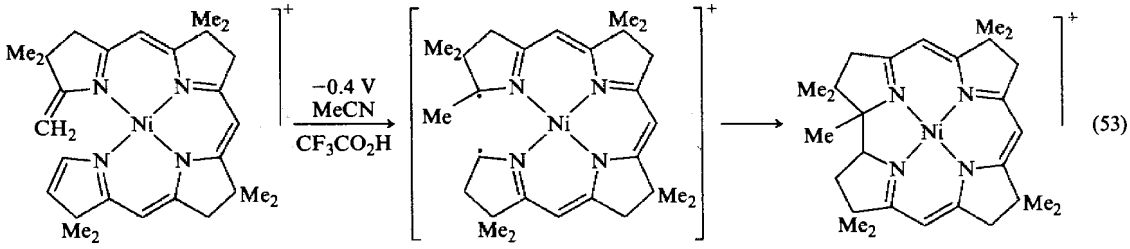
(**106**) (**107**)

Scheme 67

The secocorrin nickel complex (**101**) can also be induced to undergo an electrochemical cyclization to corrin (**100**) but only in low yield. The experimental conditions involve a one-electron oxidation, followed by a one-electron reduction.[269] The same secocorrin complex (**101**) is the starting material for two cyclization sequences leading to a didehydrocorrin complex (**107**) with a chromophore of seven double bonds (Scheme 67).[269,270] The most interesting feature of these sequences is the remarkably easy acid-catalyzed ring closure of the secocorrinoid complex (**106**) to corrin (**107**).

In consideration of a possible biosynthetic route for the corrin ring system, Eschenmoser devised a reductive, acid-catalyzed cyclization of a dehydrosecocorrinoid complex (**108**) to the corrin (**109**), possibly *via* a diradical intermediate (equation 53).[267]

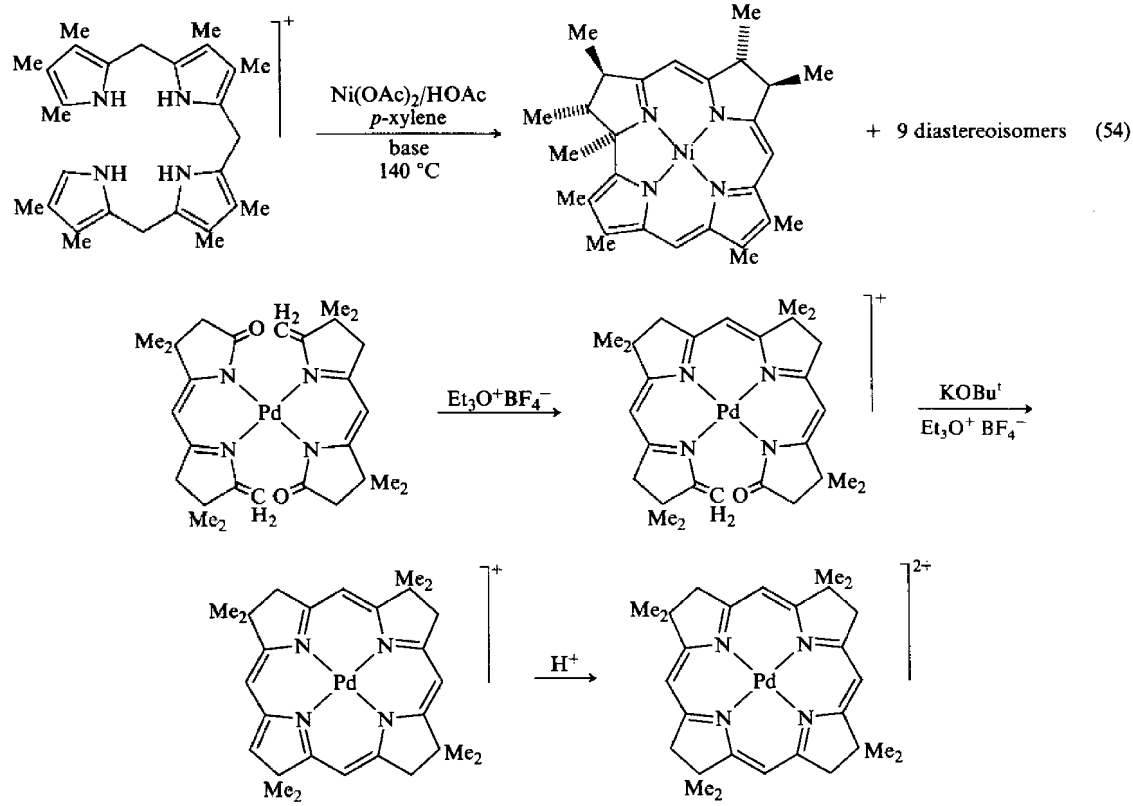
Presumably the biosynthetic pathways of the porphyrins and corrins are related to some extent, and the direct template cyclization of a tetrapyrrole has now been described to give a mixture of 10 diastereoisomers of tetradehydrocorrin complexes (equation 54).[271] In the pursuit of chemical and biosynthetic similarities and differences between corrins and porphyrins, it is necessary to



(53)

(108) (109)

develop the chemistry of reduced porphyrins. Some years ago, Eschenmoser's group reported a synthesis of corphin, a corrinoid–porphinoid ligand system containing eight conjugated double bonds in an inner 16-membered ring. The synthesis is based on an enamine–imidate cyclization (Scheme 68).[272] Very recently, a major study of reduction and oxygenation reactions of corphin complexes has been reported.[273]



Scheme 68

In many of the above cyclization reactions it is not clear to what extent the metal ion is important. In most cases a geometrical effect is significant but electronic activation is probably not always of importance. The corphin synthesis (see Scheme 68) is a good example of precise geometrical requirements. This cyclization succeeds for the palladium complex but not for nickel or cobalt complexes. The imidate condensation seems to require steric acceleration and more is provided by the desire of palladium to attain planarity than the urge for nickel or cobalt to do so.

61.1.4 REACTIONS OF COORDINATED CARBONYL COMPOUNDS

In this section the emphasis turns away from the synthesis of complex molecules which are assisted by the coordination of intermediates to metal ions, and towards reactions of relatively simpler chelates. Many examples will not be template reactions. Furthermore, the discussion will be restricted to reactions of carbonyl ligands which have proved to be of most significant synthetic utility. In many cases the utility is in the construction of more highly substituted ligands, not necessarily resulting in an increase in donor atom capacity. In some examples the free organic ligand molecule will be the desired synthetic goal, and stereoselectivity will at times be of impor-

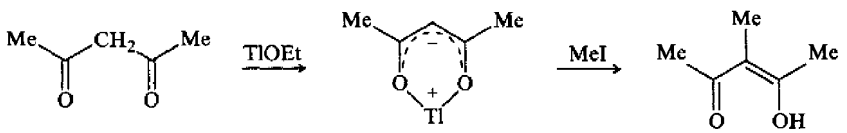
tance. In this respect it is perhaps worth drawing attention to the fact that only stoichiometric and not catalytic reactions are dealt with in this discussion.

A somewhat arbitrary selection of areas is based on their perceived synthetic utility. β-Diketone and α-amino acid chelate reactions have received much attention over the years and the latter are still at the forefront of current activity. Finally, some reactions of simple ketones are affected by metal coordination and this subject will also be considered.

61.1.4.1 β-Diketones

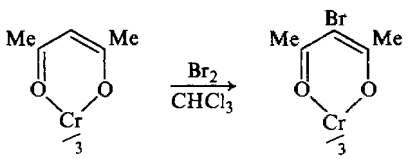
The β-diketonate chelate complexes are very stable and exhibit properties which are rather typical of aromatic systems. Many of their reactions such as halogenation, alkylation and acylation can be compared with those of the β-diketonate anions associated with alkali metal cations. However, complexes of transition and other metals add to the stability of the system, so that quite vigorous reaction conditions can be employed. In most of the work carried out on β-diketonate chelates, the modified ligand has not been removed from the metal ion, but this can usually be effected if desired.

One example of such a reaction sequence employs thallium(I) as the coordinating metal and allows clean alkylation of a β-diketone to be carried out (Scheme 69).[274,275] This technique has become an established part of synthetic organic methodology.

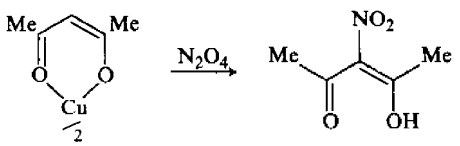


Scheme 69

The first report of a coordinated acetylacetone reaction was the bromination of the chromium(III) complex (equation 55).[276] This was followed, more than 30 years later, by the nitration of copper(II) acetylacetonate with dinitrogen tetroxide (equation 56).[277] This result is significant in that the normal organic nitration conditions are too acidic to effect nitration without disruption of the chelate ring. In general, reaction conditions must be chosen with care, to allow the ligand transformation to occur on a stable chelate ring. The kinetically stable chromium(III), cobalt(III) and rhodium(III) tris(acetylacetonates) are the most suitable complexes and have consequently been studied most thoroughly. However, complexes of beryllium(II), copper(II), nickel(II), platinum(II), iron(III), aluminum(III) and europium(III) have also been submitted to a variety of substitution reactions.



(55)

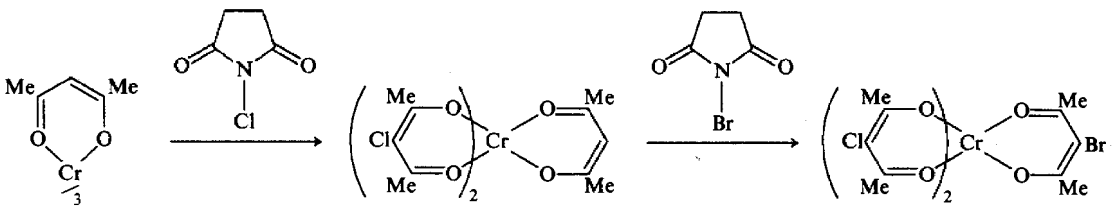


(56)

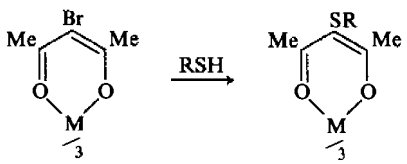
Halogenation can best be effected by *N*-halosuccinimides, with bromination being much faster than chlorination or iodination.[278] No reaction occurs on the methyl groups and it is most likely that the mechanism is ionic rather than radical. Partial bromination can lead to a mixture of mono-, di- and tri-brominated chelates, showing that bromination of one chelate ring has an effect on the bromination of the second one, and so on. As a result of the great stability of acetylacetonate complexes, product mixtures can be separated by chromatography.[279] Mixed halogenation products can be obtained by a sequence of steps (Scheme 70).

The brominated chelates are chemically much less reactive than the organic ligands themselves. Most nucleophilic substitution reactions are ineffective, but bromine can be displaced by thiols (equation 57).[280] The halo complexes do not react with lithium or magnesium metals, but can be hydrogenolyzed to the unsubstituted complexes (equation 58).[281]

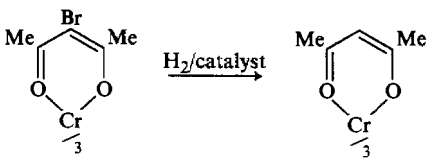
Nitrodehalogenation can be effected, as for halobenzenes, but the reaction is only moderately effective even for the most reactive iodo compounds (equation 59).[281] The reaction conditions of copper(II) nitrate and acetic anhydride are the most suitable for the general nitration of chelated



Scheme 70

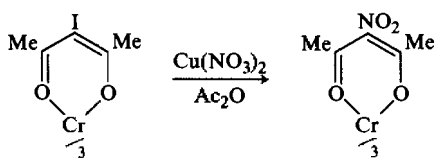


(57)

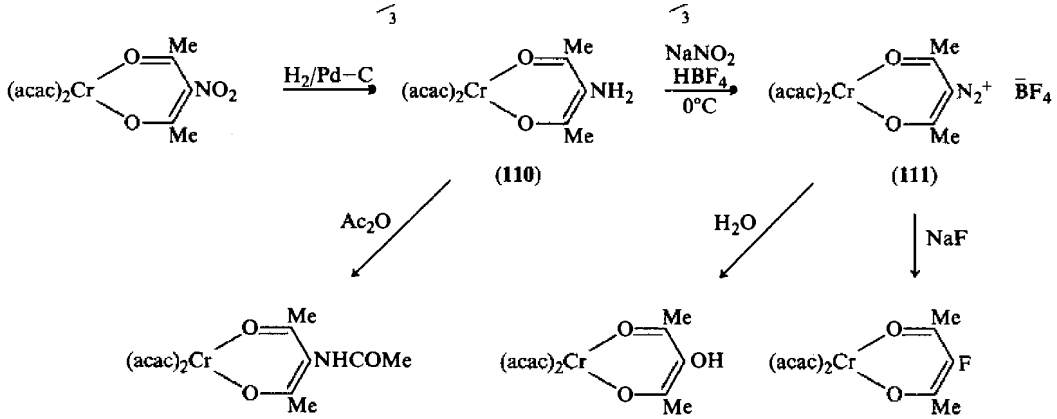


(58)

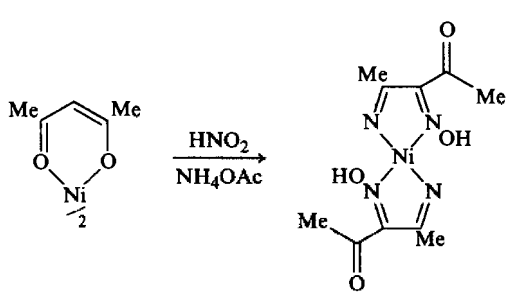
acetylacetonates.[282] Nitroacetylacetonates behave in a similar fashion to nitroarenes, undergoing catalytic reduction to the amino derivative, diazotization of the amine and typical Sandmeyer reactions of the diazonium compounds (Scheme 71).[283] The amine (**110**) behaves normally and can be acetylated. The diazonium fluoroborate (**111**) is stable in the solid state and can be characterized. Attempts to carry out nitrosation on a nickel(II) acetylacetonate led to a rather extensive rearrangement process (equation 60).[284]



(59)



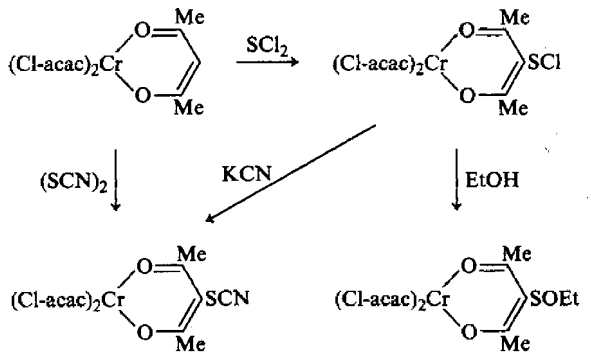
Scheme 71



(60)

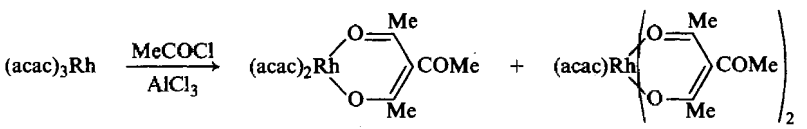
Carbon–sulfur bonds can be formed by electrophilic substitution of acetylacetonates with sulfur dichloride or thiocyanogen and the chlorosulfur group can be readily transformed by nucleophilic displacement of chloride ion (Scheme 72).[285,286]

Friedel–Crafts acylation of even the kinetically stable acetylacetonates can only be carried out with difficulty and with the use of vigorous conditions. A mixture of boron trifluoride etherate

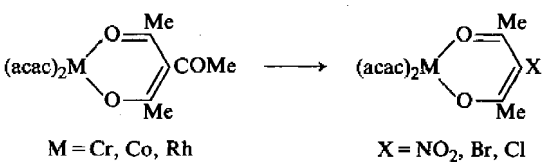


Scheme 72

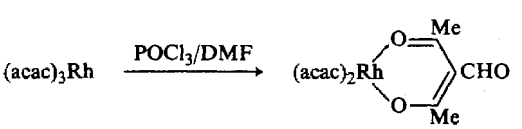
and acetic anhydride acetylates the cobalt(III) and chromium(III) chelates, but has no effect on the rhodium(III) complex. A more powerful mixture of acetyl chloride and aluminum chloride acetylates the rhodium chelate but destroys the acetylated cobalt and chromium derivatives. The introduction of an acetyl group results in a deactivation of the remaining rings, so that product mixtures are formed and trisacetylation is only achieved in low yield for the cobalt and chromium complexes and not at all for the rhodium chelate (equation 61).[286] Groups larger than acetyl can be introduced only with difficulty and usually only to yield the monosubstituted complex. Nitrodeacylation and halodeacylation can be carried out very effectively, but are not of great synthetic value (equation 62).[281] Vilsmeier formylation can be carried out successfully to yield monoaldehydes, but further transformation of the aldehyde group is thwarted by steric hindrance (equation 63).[281]



(61)

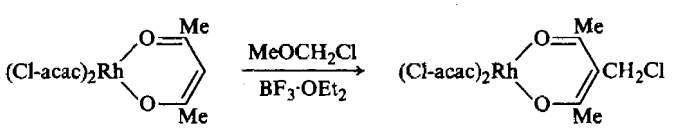


(62)

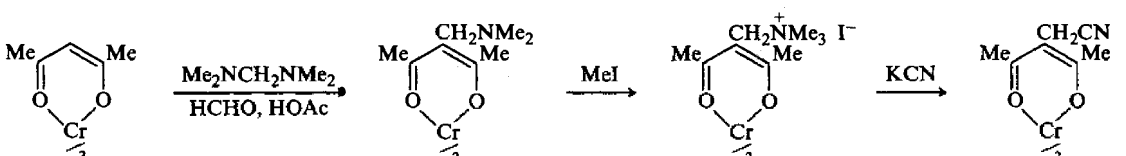


(63)

Alkylation of acetylacetone chelates is generally unsuccessful, but carbon–methylene bonds can be formed by chloromethylation,[279] reaction with ethyl diazoacetate,[287] reaction with thioacetals[288] (equations 64, 65 and 66) and by the Mannich reaction (Scheme 73).[279] The Mannich base can be quaternized with methyl iodide and converted by cyanide ion into a cyanomethyl-substituted chelate.

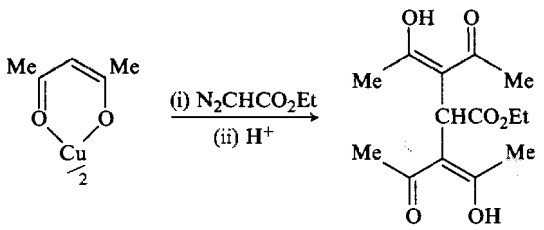


(64)

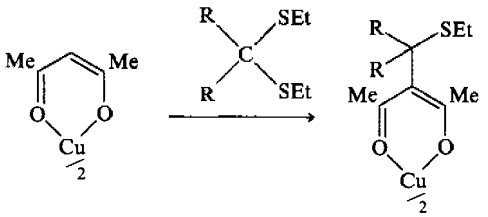


Scheme 73

The methyl groups in acetylacetone chelates appear to enhance electronically the reactivity of the central carbon position and this overcomes the steric retardation which they cause. The formylacetone and malondialdehyde chromium(III) chelates undergo the typical bromination and nitration reactions more slowly than does the acetylacetone chelate and the products are less stable

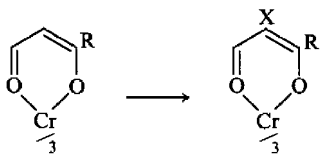


(65)



(66)

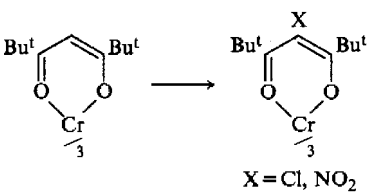
(equation 67).[289] The related rhodium and cobalt complexes cannot be prepared because of internal redox reactions between the aldehyde ligand and the metal ion.



(67)

R = H, Me X = Br, SCN, NO_2

The replacement of methyl groups on acetylacetone by *t*-butyl groups causes a massive increase in steric hindrance to electrophilic substitution. The chromium(III) chelate of dipivaloylmethane can be chlorinated and nitrated only very slowly by means of forcing conditions (equation 68).[281]



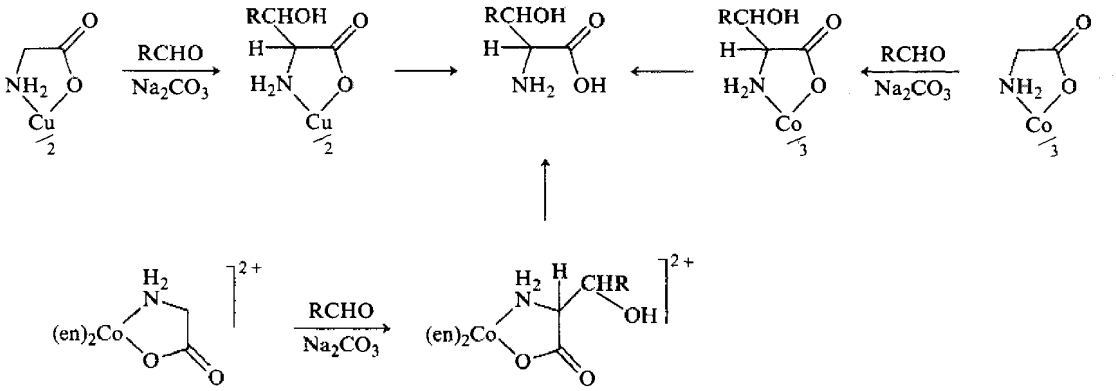
(68)

X = Cl, NO_2

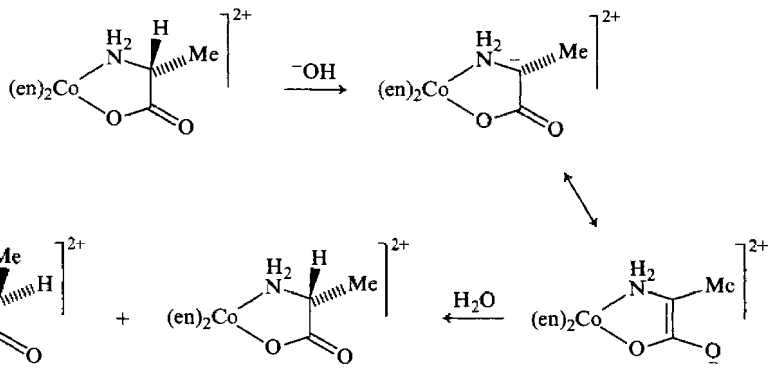
61.1.4.2 α-Amino Acids and their Imine Derivatives

The chemical reactivity of coordinated glycine and other α-amino acids towards formaldehyde and other aldehydes in alkaline conditions has been under investigation for many years, since the initial work by Sato, Okawa and Akabori.[290] While most of the work has been carried out on copper(II) complexes, some more recent studies on cobalt(III) systems have been made (Scheme 74).[291–295] In the majority of investigations the complexes resulting from the aldol condensation have been decomposed to yield β-hydroxy-α-amino acids. The most significant feature of these reactions is the formation of a methylene carbanion adjacent to the protected amino and carboxylate functions. Thus proton exchange takes place readily and consequently leads to racemization of optically active α-amino acids (Scheme 75).[296,297] The dissymmetric nature of cobalt(III) amino acid complexes also enables asymmetric induction and this has been studied with respect to deuteration[298] and aldol condensation.[299] It has been found in the case of peptides that selective proton exchange occurs on the methylene group of the terminal amino acid.[300,301] Small peptides such as glycylglycine and glycylglycylglycine have been converted to *N*-terminal β-hydroxy amino acids by the reaction of their copper(II) complexes with aldehydes.[302,303]

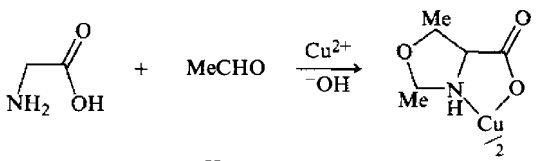
In addition to the attack of amino acid methylene carbanions on aldehydes, occasionally the amino nitrogen atom also acts as a nucleophile. For example, the reaction of glycine with acetaldehyde in the presence of basic copper(II) carbonate gives an oxazolidine complex (equation 69).[304] Similarly, reaction of the serinatocopper(II) complex (**112**) with excess formaldehyde gives rise to initial reaction at nitrogen, as shown by the intermediate (**113**), followed by reaction at carbon and then nitrogen again. The resulting complex (**114**) could be converted into hydroxymethylserine and the bicyclic product (**115**) (Scheme 76).[305] Another reaction involving attack at nitrogen is that of amino acid copper(II) complexes with phosgene, giving rise to an oxazoline dione (equation 70).[306]



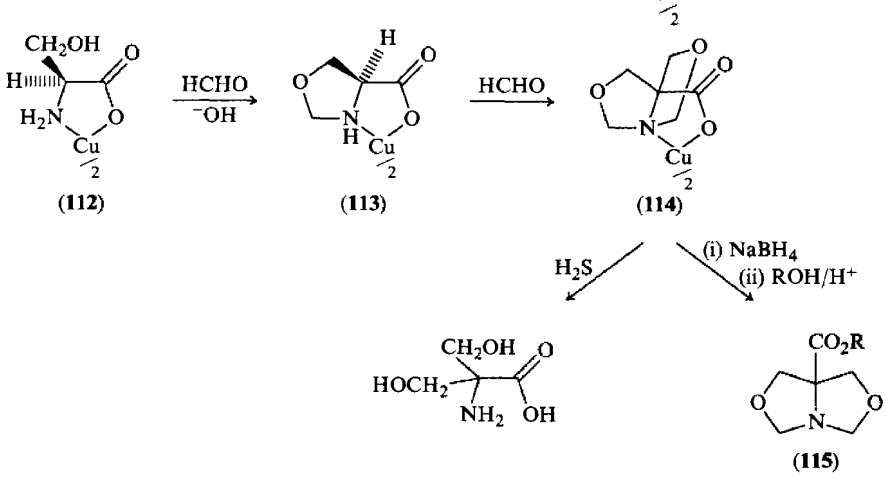
Scheme 74



Scheme 75



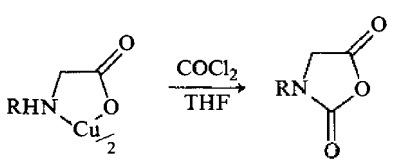
(69)



(112) **(113)** **(114)**

(115)

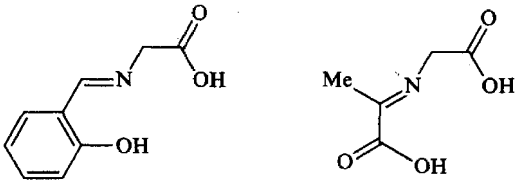
Scheme 76



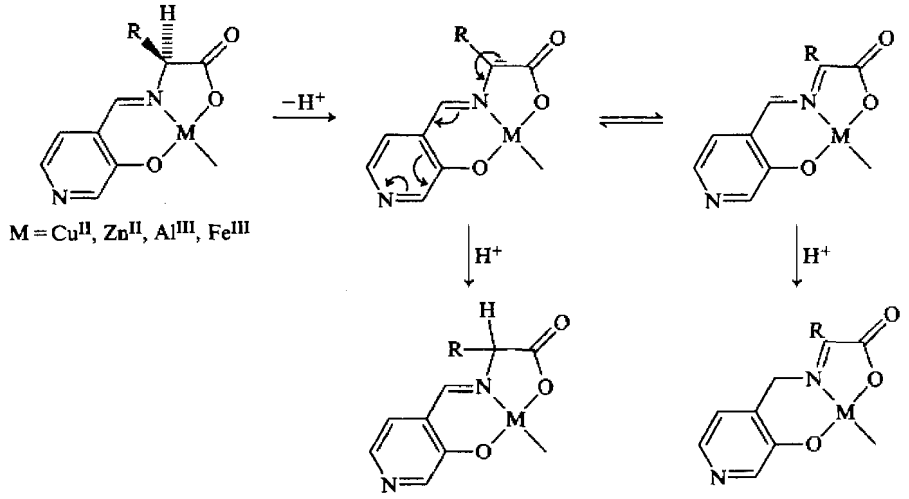
(70)

The kinetic acidity of the methylene protons on coordinated amino acid fragments is enhanced in imine complexes such as those derived from the ligands **(116)**[307] and **(117)**.[308] This enhanced acidity is responsible for both racemization[309,310] and transamination[311–313] processes, which have been studied in detail because of the biologically important pyridoxal-activated enzyme

reactions.[314] Imine isomerization is the crucial feature of the process, which is summarized in a simplified form in Scheme 77.



(116) (117)

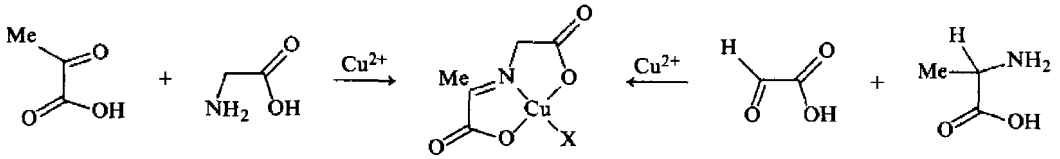


M = Cu^{II}, Zn^{II}, Al^{III}, Fe^{III}

racemic

Scheme 77

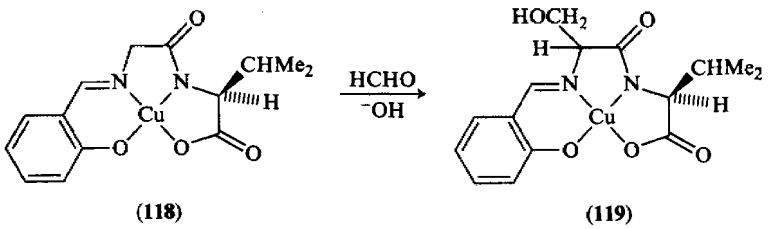
In model experiments, the same imine complexes are formed from the two possible combinations of starting materials, as shown for the pyruvate example in Scheme 78.[315]



Scheme 78

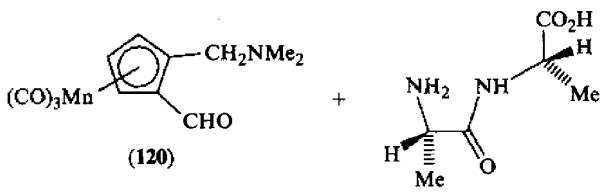
Stereoselectivity is enhanced in reactions of amino acid imine complexes of salicylaldehyde or pyridoxal. For example, the chiral complex (**118**), incorporating glycylvaline into its imine ligands, undergoes reaction with formaldehyde to give complex (**119**) in which the new seryl fragment is optically active (equation 71).[316] Enantioselectivity of carbon–carbon and carbon–deuterium bond formation has also been observed with cobalt(III) complexes, which bring about asymmetric induction as a result of the chiral arrangement of ligands.[317–319] Although this technique provides the basis for an asymmetric synthesis of amino acids, removal of the ligand from the cobalt ion results in a loss of the chirality conditioned by the spatial arrangement of ligands about cobalt. Consequently, incorporation of a chiral aldehyde into an amino acid imine complex allows the chiral fragment to be preserved after isolation of the amino acid, and therefore used repeatedly for asymmetric transformations. An example of such a chiral aldehyde is the organomanganese compound (**120**), which can be resolved into its enantiomers by formation and separation of diastereomeric imine complexes with optically active dipeptides such as (*S*)-Ala-(*S*)-Ala (Scheme 79).[320] The enantiomeric aldehydes can then be incorporated into imine complexes of glycylglycine, which on treatment with acetaldehyde, followed by hydrolysis, afford high asymmetric yields of the enantiomeric threonines and allo-threonines (Scheme 80).[320]

Another chiral aldehyde suitable for such transformations is the recently prepared pyridoxal derivative (**121**).[321] Even more recent examples of chiral carbonyl compounds (**122**) have been used for the partial resolution of amino acids. The enantiomers of compounds (**122**) undergo reaction with racemic α-amino acids and copper(II) ions to give preferential formation of enantiomeric copper complexes. The (*S*)-enantiomers of (**122**) preferentially form complexes containing the

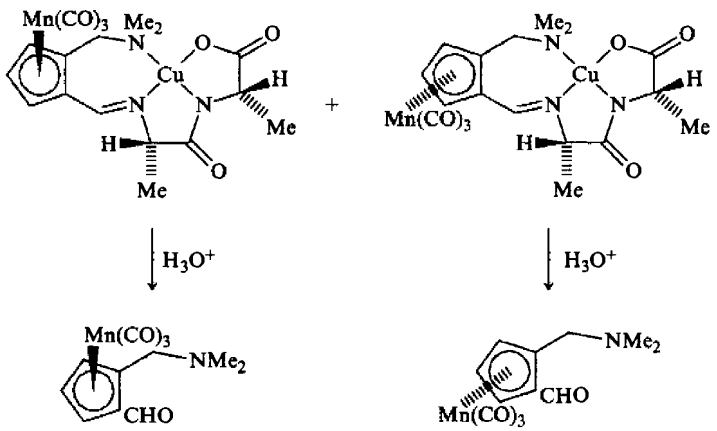


(71)

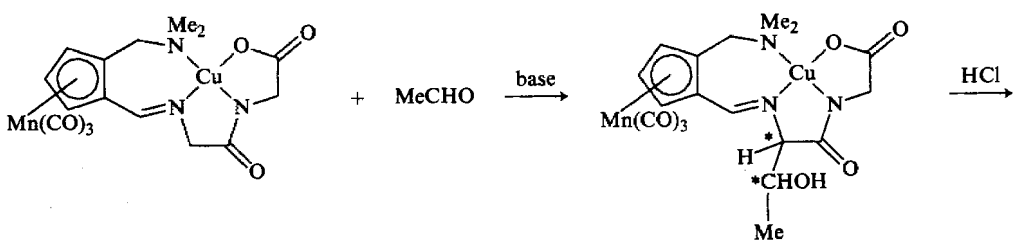
(118) (119)



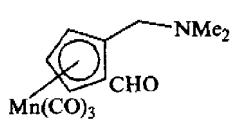
(120)



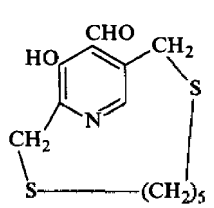
Scheme 79



H-Thr-Gly-OH + allo-H-Thr-Gly-OH +



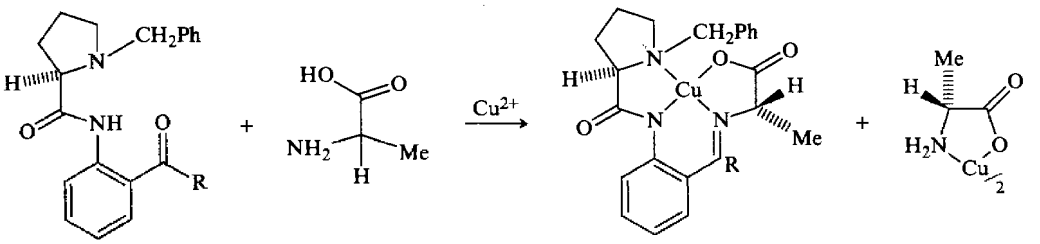
Scheme 80



(121)

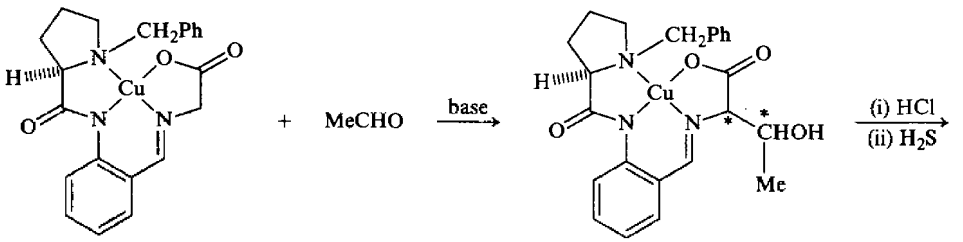
(*S*)-amino acid. The (*R*)-enriched enantiomer is present in solution after isolation of the (*S*)-enriched complex (Scheme 81).[322] The similar quadridentate complexes of the glycinimine can be converted to the hydroxyethyl derivative by reaction with acetaldehyde. In this case the (*S*)-en-

antiomers of the carbonyl compounds (**122**) give rise to a mixture of diastereomeric complexes, which on removal of copper(II) ions give (*R*)-threonine of high enantiomeric purity and a substantial excess of threonine over allo-threonine (Scheme 82).[322]



(**122**) R = H or Me

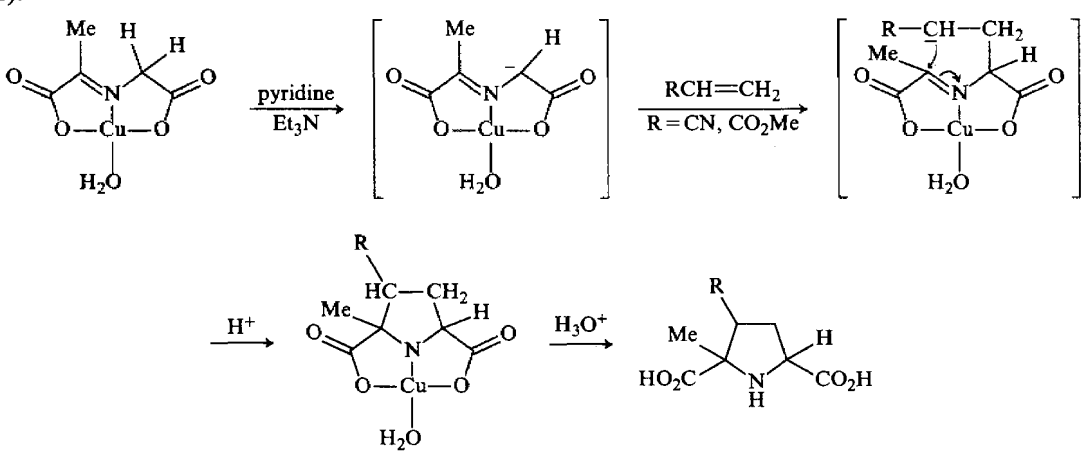
Scheme 81



CuS + *S*-(**122**) + H-Thr-OH + allo-H-Thr-OH

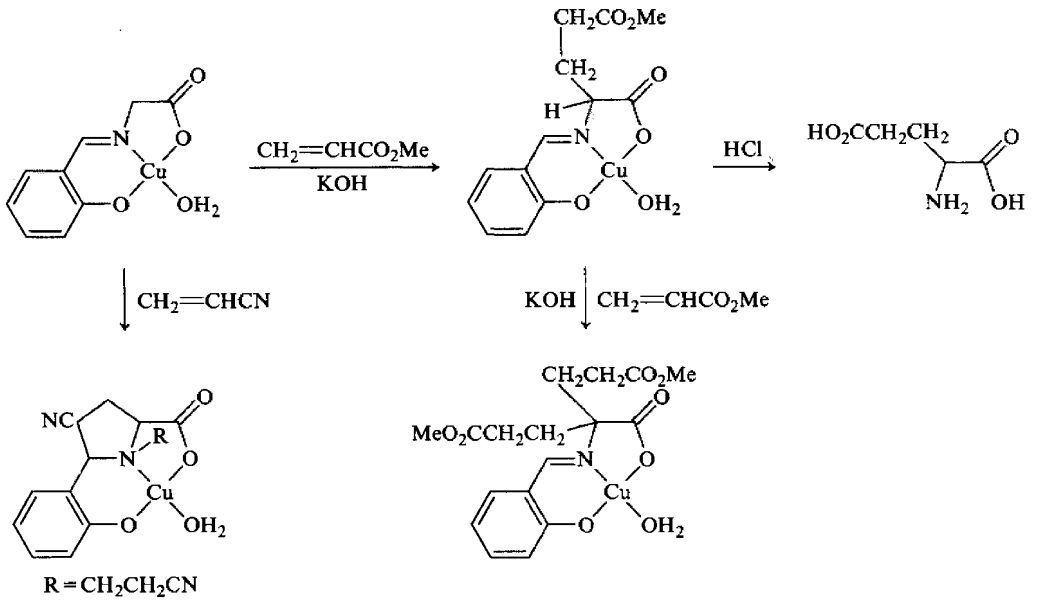
Scheme 82

The previous reactions have involved the addition of a methylene carbanion on to an aldehyde carbon atom. The copper(II) complex of the pyruvate imine ligand (**117**) undergoes Michael addition under basic conditions to acrylonitrile and methyl acrylate and cyclization occurs on to the imine carbon atom. Hydrolysis of the resulting complex gives the respective proline derivatives (Scheme 83).[323] This is the latest and most useful outcome of reactions of this type. In earlier experiments, Belokon' and his group found that carbanion addition of the copper(II) complex of the salicylidenimine ligand (**116**) to methyl acrylate occurred without cyclization and provided a route to glutamic acid,[324] whereas Casella and coworkers obtained a cyclization product from acrylonitrile (Scheme 84).[325] Even simple base-promoted alkylation of the copper(II) complex of the salicylidene glycine ligand (**116**) can be achieved, though not in very good yields (equation 72).[326]

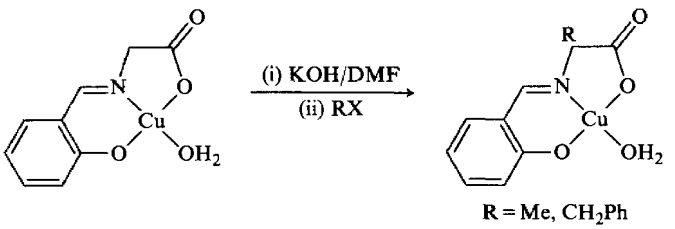


Scheme 83

Sargeson and his group have recently carried out the formylation of coordinated glycine using the Vilsmeier reagent. Initially, an unusually stable iminium derivative was formed and shown to be the (*Z*)-isomer (**123**). A small amount of the corresponding (*E*)-isomer was also detected but was observed to undergo rapid hydrolysis to the formylglycine complex.[327] The (*Z*)-isomer can also be converted to the formylglycine complex (**124**) by treatment with concentrated sulfuric acid followed by water (Scheme 85).[328] The aldehyde complex (**124**) is hydrated in the solid state, but

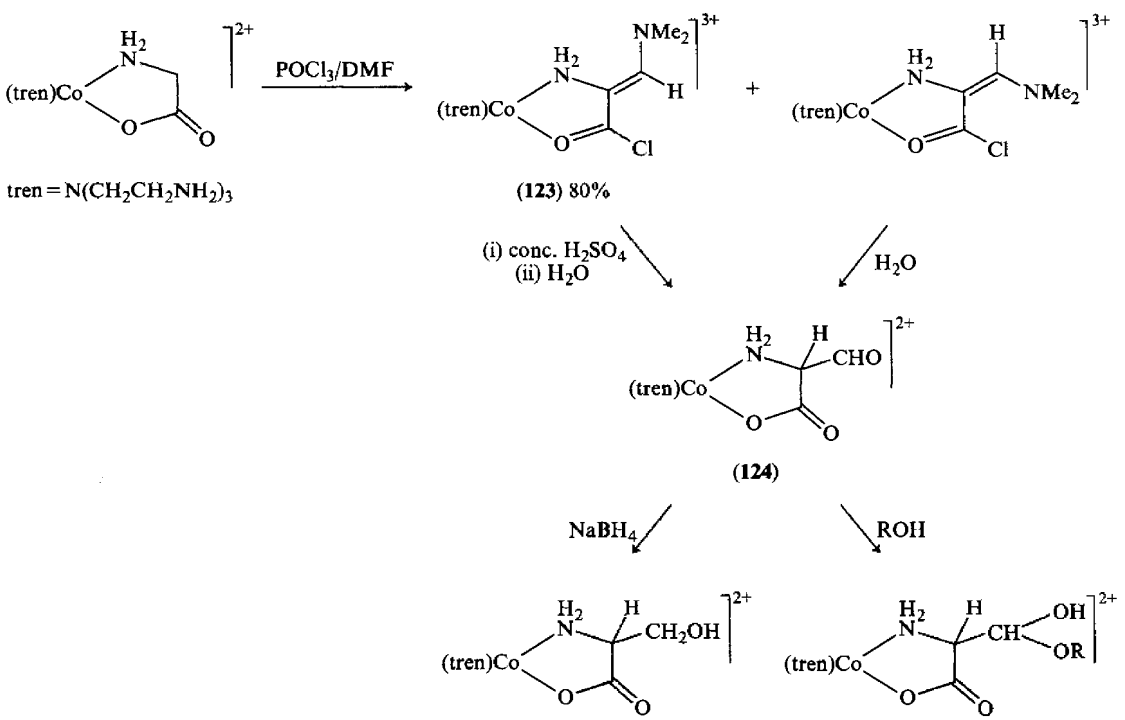


Scheme 84



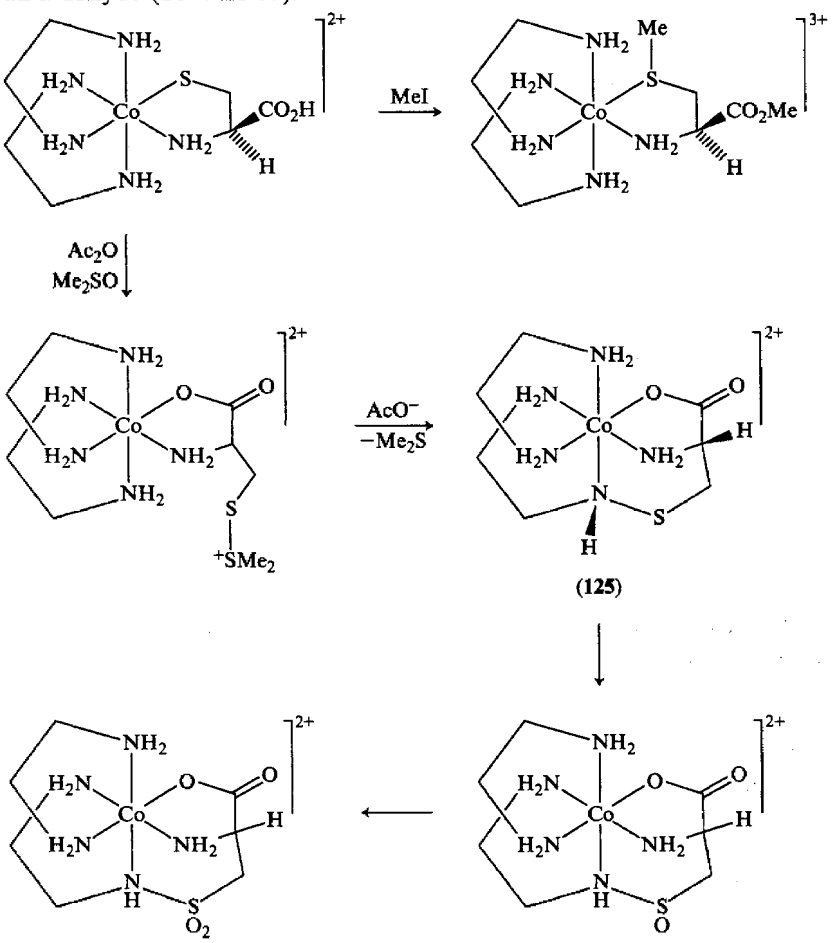
(72)

in solution forms an equilibrium mixture of aldehyde and hydrate, and consequently undergoes typical aldehyde reactions, such as reduction and hemiacetal formation. The borohydride reduction is of particular synthetic interest, as it provides a useful preparation of serine from glycine, as the yields in all steps are very high. The formyl glycine complex (**124**) is analogous to the protected formyl glycine used as a key intermediate in the total synthesis of penicillins.



Scheme 85

The α-amino acid cysteine exhibits different coordination properties to the simpler amino acids which do not contain sulfur. Coordination to cobalt(III) occurs *via* nitrogen and sulfur donor atoms, leaving the carboxyl group free. The coordinated sulfur atom can be methylated[329] and treatment of the complex with dimethyl sulfoxide and acetic anhydride initiates a rearrangement to an aminocarboxylate chelate ring, with an appended methylene disulfide chain. A stereospecific cyclization then occurs to produce a complex (**125**) containing a new chelate ring and an unusual new quadridentate ligand (Scheme 86).[330] This ligand can be oxidized at sulfur to the sulfoxide and sulfone derivatives,[331] a reaction reported much earlier for tris(cysteinato)cobalt(III).[332] The nitrogen–sulfur bond of complex (**125**) can be cleaved by nucleophilic attack at sulfur. Cyanide ion forms a thiocyanate which is itself stereoselectively attacked by a neighbouring amide anion to produce an aminothiazoline ring (Scheme 87).[333] Hydride reduction of (**125**) reproduces the free mercapto group, and cyclization to yield a thiazolidine ring can be achieved by base-promoted reaction with an aldehyde (Scheme 87).[334]

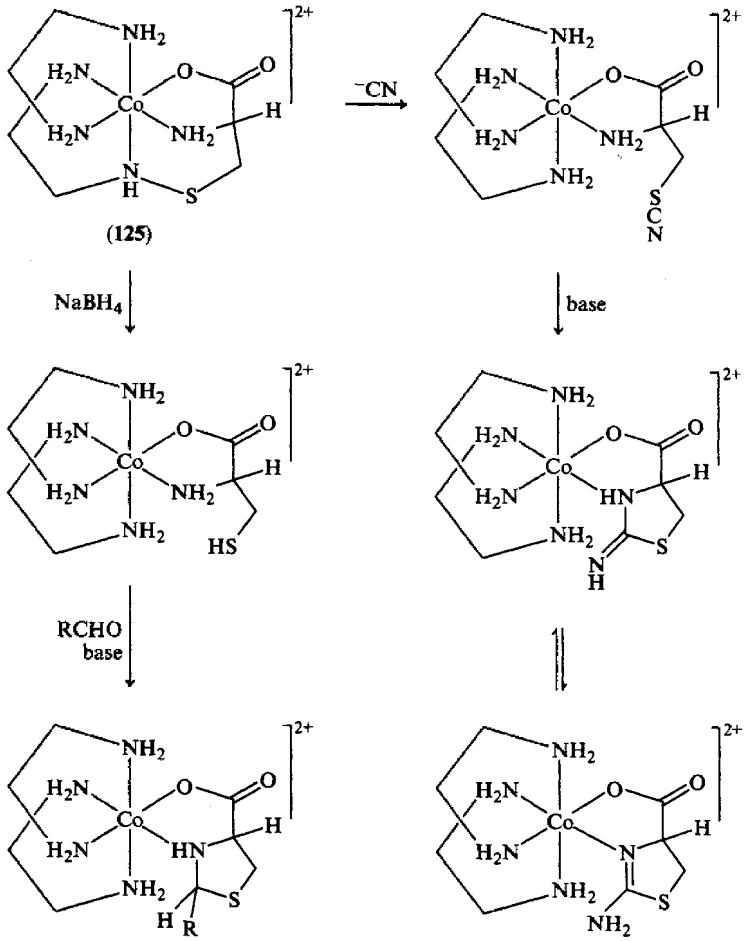


Scheme 86

61.1.4.3 α-Amino Acid Carboxylate Derivatives

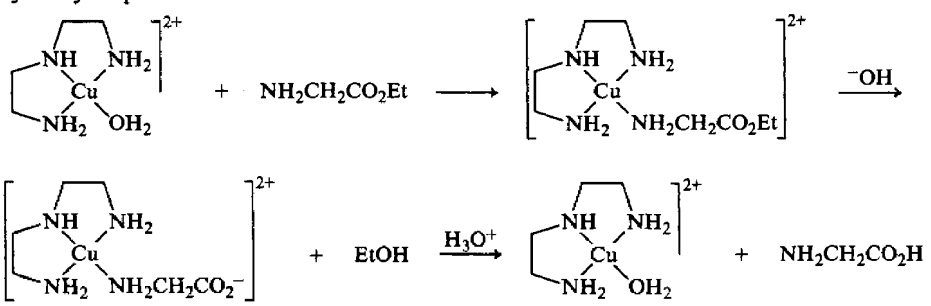
The most extensively studied reactions of coordinated amino acid derivatives are those involving nucleophilic attack at the carbonyl group. These aspects, as well as some of those already covered in the previous section, have been reviewed.[335–337] Mechanistic aspects of these reactions have also been discussed in Chapter 7.4. The emphasis in this section will be on the synthetic value of stoichiometric reactions of this type. The two most important synthetic processes are peptide hydrolysis and peptide synthesis, both involving the same mechanism.

It has been known for many years that the rate of hydrolysis of α-amino acid esters is enhanced by a variety of metal ions such as copper(II), nickel(II), magnesium(II), manganese(II), cobalt(II) and zinc(II).[338] Early studies showed that glycine ester hydrolysis can be promoted by a tridentate copper(II) complex coupled by coordination of the amino group and hydrolysis by external hydroxide ion (Scheme 88).[339] Also, bis(salicylaldehyde)copper(II) promotes terminal hydrolysis of the tripeptide glycylglycylglycine (equation 73).[340] In this case the *N*-terminal dipeptide fragment

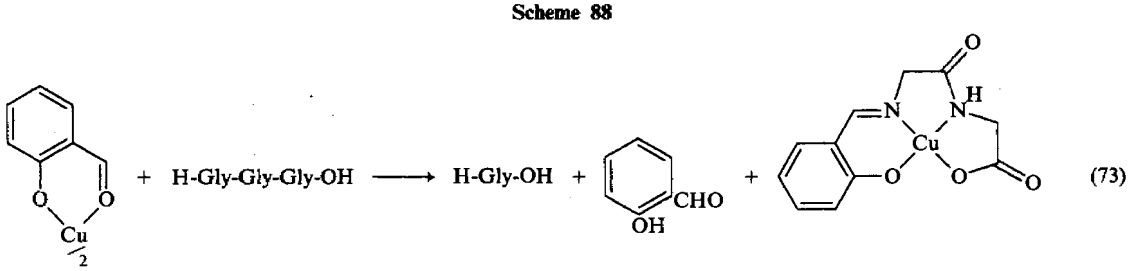


Scheme 87

becomes coordinated to the copper(II) ion *via* an imine ligand, leaving the *C*-terminal glycine as the free hydrolysis product in solution.



Scheme 88

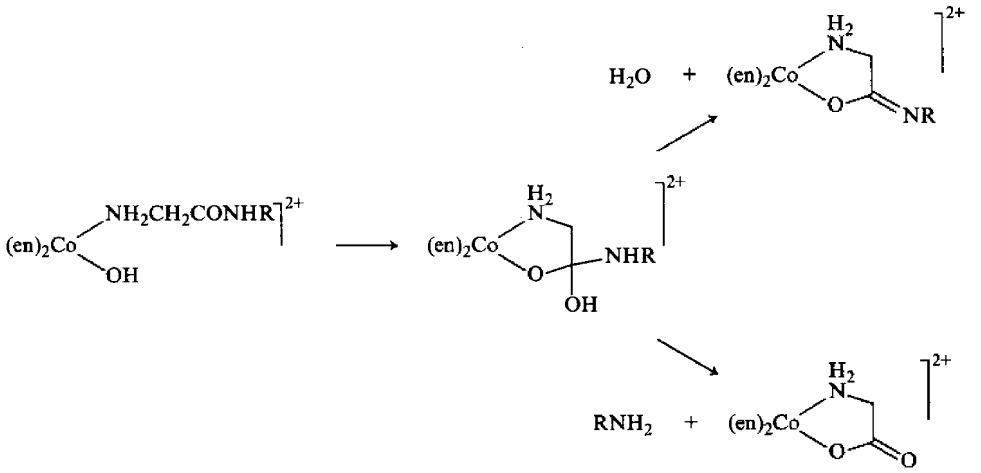


(73)

Many more recent stoichiometric studies of cobalt(III) complexes have been responsible for most of the developments in this area of research. Cobalt(III) ammine complexes effect hydrolysis of ethyl glycinate in basic conditions *via* intramolecular attack of a coordinated amide ion; hydrolysis by external hydroxide ion attack also occurs (equation 74).[341] Replacement of ammonia ligands by a quadridentate or two bidentate ligands allows the formation of aquo-hydroxo complexes and enables intramolecular hydroxide ion attack on a coordinated amino ester, amino amide

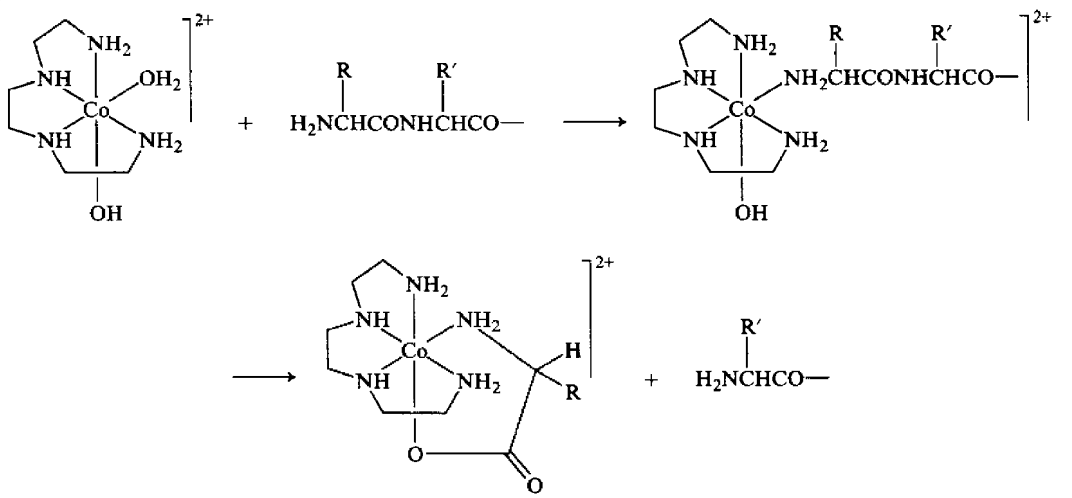
or peptide. The reaction process is shown for a bis(1,2-diaminoethane) complex (Scheme 89).[342–345] In general, the rate-determining step is the initial cyclization.

$$2[(NH_3)_5CoNH_2CH_2CO_2Et]^{3+} \xrightarrow{^-OH} [(NH_3)_4CoNH_2CH_2CONH]^{2+} + 2EtOH + [(NH_3)_5CoNH_2CH_2CO_2]^{2+} \quad (74)$$



Scheme 89

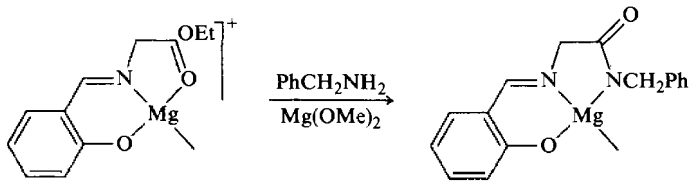
A detailed investigation of configurational isomers has been carried out with a view to the development of a peptide sequencing process.[346] Quite good developments towards a practical sequencing process have been made using simple peptide cobalt(III) complexes of triethylenetetramine and tris(2-aminoethyl)amine (Scheme 90).[347–349] The critical *N*-terminal complexes can be generated from both aquo-hydroxo or dichloro complexes. Extension to polypeptide sequencing[350–352] has been less successful as it appears that side-chain coordination interferes, the *N*-terminal selectivity is not as high as it is in simple cases and there are separation problems.[349,353,354]



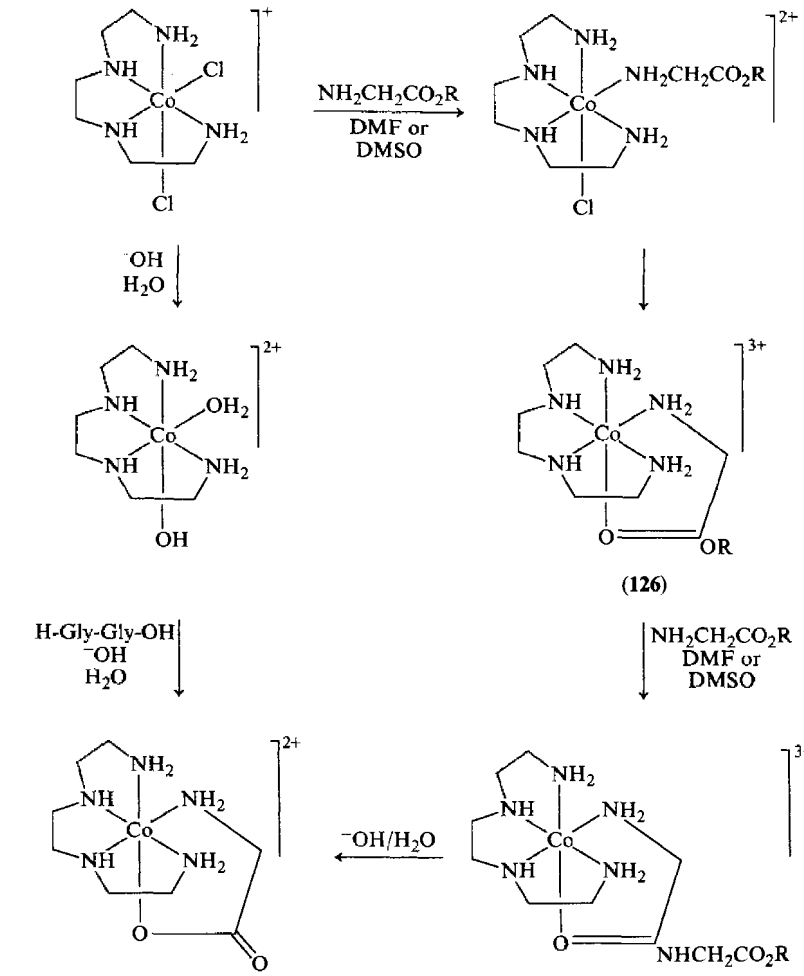
Scheme 90

Coordinated α-amino amides can be formed by the nucleophilic addition of amines to coordinated α-amino esters (see Chapter 7.4). This reaction forms the basis of attempts to use suitable metal coordination to promote peptide synthesis. Again, studies have been carried out using coordination of several metals and an interesting early example is amide formation on an amino acid imine complex of magnesium (equation 75).[355] However, cobalt(III) complexes, because of their high kinetic stability, have received most serious investigation. These studies have been closely associated with those previously described for the hydrolysis of esters, amides and peptides. Whereas hydrolysis is observed when reactions are carried out in water, reactions in dimethylformamide or dimethyl sulfoxide result in peptide bond formation. These comparative results are illustrated in Scheme 91.[356–358] The key intermediate (**126**) has also been reacted with dipeptide

esters to give coordinated tripeptide esters. A detailed mechanistic investigation of this type of reaction has established the intermediacy of an amine–alcohol complex.[359]



(75)

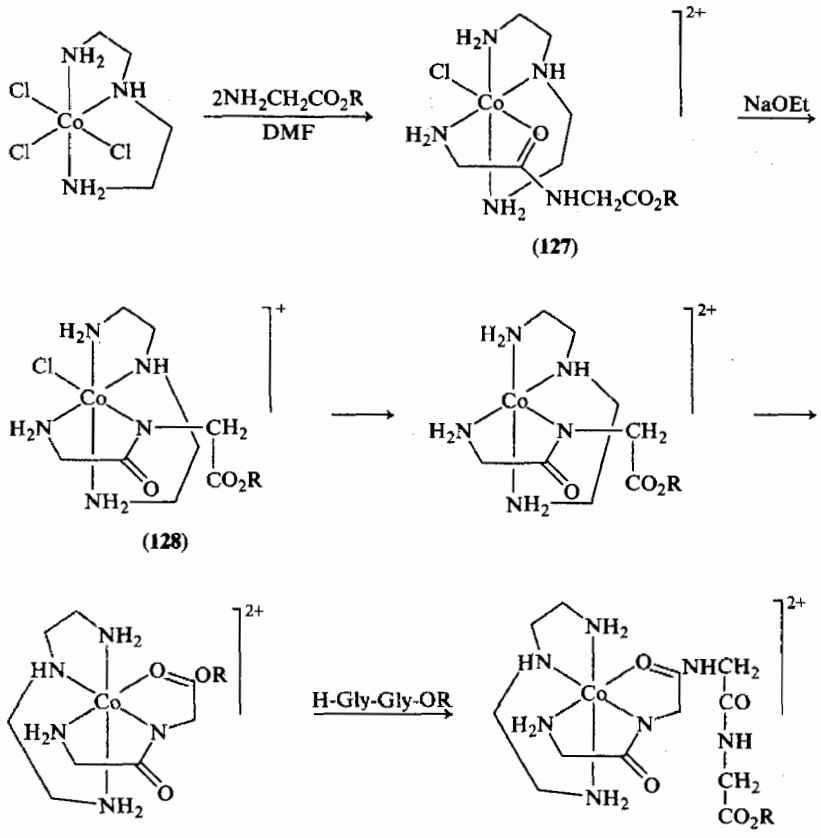


Scheme 91

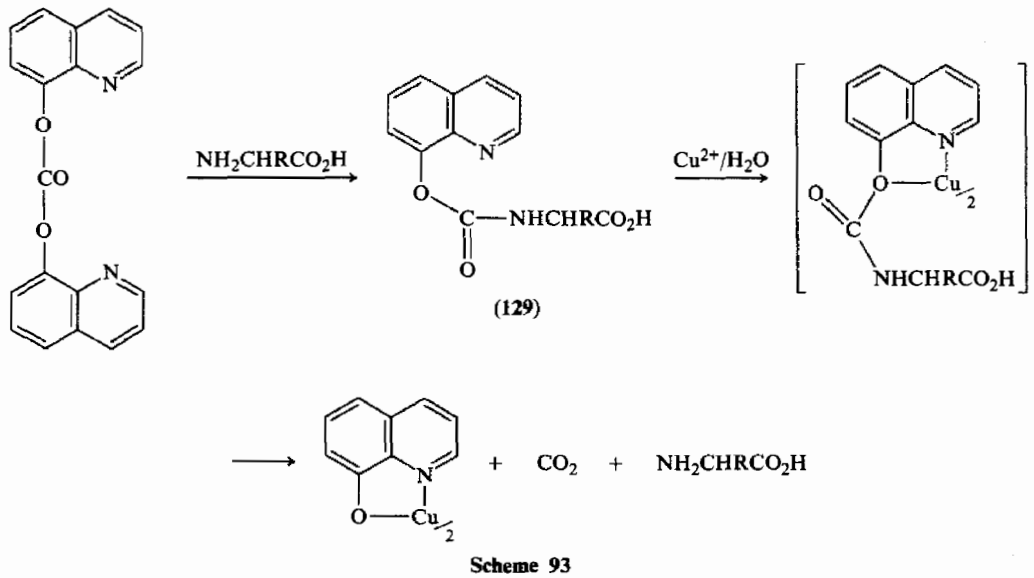
A three-site system for peptide synthesis around a cobalt(III) complex has been studied. Instead of a quadridentate ligand as used in the above experiments, Wu and Busch chose the tridentate ligand diethylenetriamine. The formation of dipeptide and tetrapeptide complexes is shown in Scheme 92.[360] The ester carbonyl group in the *O*-bonded amide intermediate (**127**) cannot be activated by coordination because it cannot reach the metal ion. Isomerization to the *N*-bonded amide complex (**128**) occurs with base and enables coordination and therefore activation of the ester carbonyl group.

This type of chemistry has not been developed further into an efficient peptide synthesis involving *N*-terminal addition of amino acid residues to peptide esters. The main problems are concerned with the removal of the synthesized peptide from the cobalt(III) ion without causing racemization of chiral centres or hydrolysis of peptide linkages.

In a different context, an 8-quinolyloxycarbonyl group has been used for the *N*-terminal protection of amino acids in a model peptide synthesis. At the completion of the synthesis the protecting group could be removed by coordination to copper(II) ions (Scheme 93).[361] However, this method suffers from the high reactivity of the intermediate (**129**) and has not been developed into a useful synthetic method.



Scheme 92

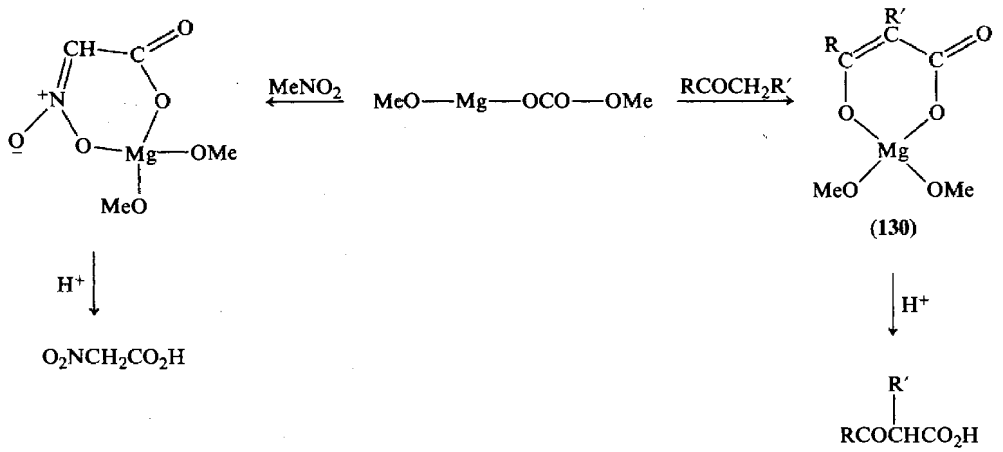


Scheme 93

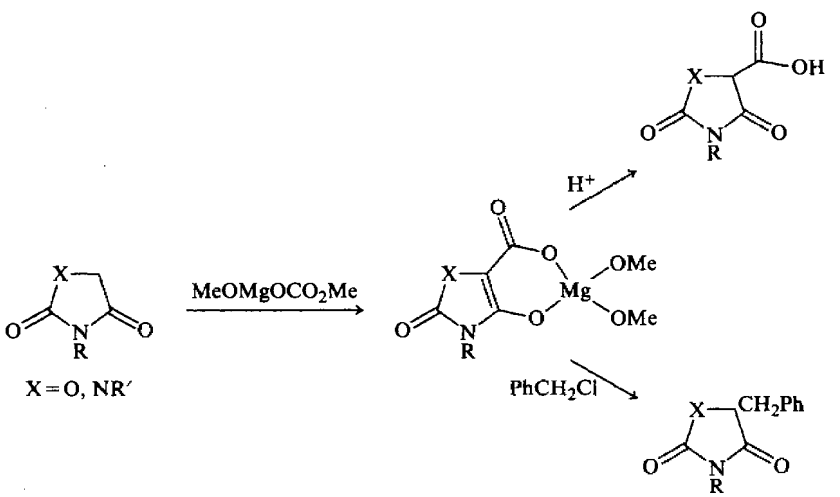
61.1.4.4 Simple Ketones and Derivatives

In this section, consideration switches to several very important organic reactions of carbonyl compounds which are not normally thought of as reactions of coordinated ligands. However, recent developments have resulted from a closer investigation of the chelating nature of intermediates and transition states.

An earlier series of experiments established useful synthetic transformations involving carboxylation of ketones and nitroalkanes to yield β-keto acids and α-nitro acids respectively (Scheme 94).[362,363] The reagent is methylmagnesium carbonate and the intermediate (**130**) can be alkylated with concomitant decarboxylation to provide greater versatility. These reactions can also be extended to ketone functions in imidazoline- and oxazolidine-diones (Scheme 95).[364,365]



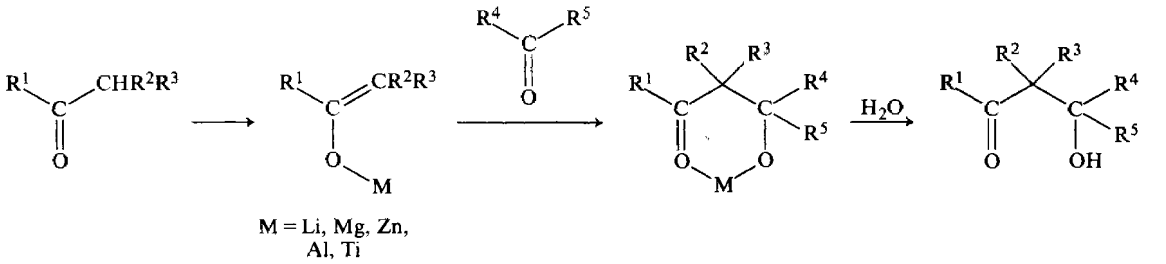
Scheme 94



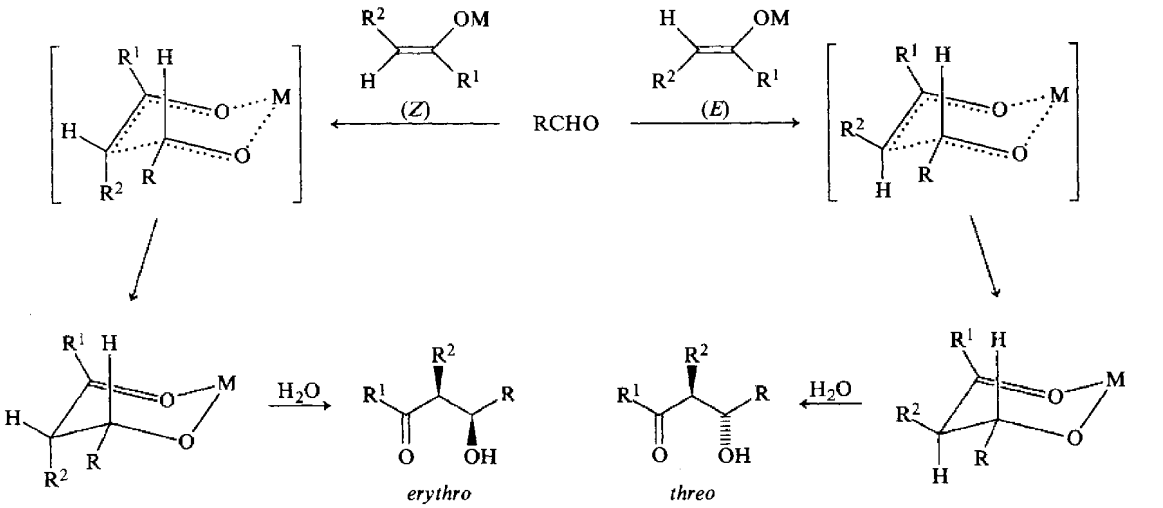
Scheme 95

The crossed aldol reaction between metal enolates and aldehydes occurs with a high degree of regiospecificity, as a consequence of the reaction proceeding *via* a chelate intermediate or transition state. The process has been reviewed recently[366] and is summarized in Scheme 96. The success of the reaction depends upon the chelation of the aldol adduct by a metal such as lithium, magnesium, zinc, aluminum or titanium. The precise geometry of the enolate salt is important in the determination of the stereochemistry of the aldol product. The other important factor is the nature of the reaction conditions with respect to the presence of kinetic or thermodynamic control. Under kinetic control the product is dependent on the geometry of the starting enolate, with the (*Z*)-enolate giving the *erythro* isomer and the (*E*)-enolate the *threo* isomer (Scheme 97). The *threo* isomer is formed preferentially under thermodynamic control, as its metal chelate precursor is more stable than the precursor of the *erythro* isomer, having the maximum number of equatorial substituents. The degree of stereoselectivity increases with the bulkiness of the aldehyde R group. Examples of lithium enolate reactions under kinetic control are shown in Scheme 98.[367] The comparison between kinetic and thermodynamic control is illustrated for a magnesium enolate in Scheme 99.[368] Aluminum enolates appear to undergo reaction with aldehydes under kinetic stereoselection, although available data are limited.[369] Zinc enolates have been implicated in the Reformatsky reaction of α-bromo esters and have recently been used for directed aldol reaction of γ-lactones with aldehydes.[370] Zinc enolates are often formed from lithium enolates but are less reactive and require a large excess of aldehyde and longer reaction times (Scheme 100).[371] Zinc enolates of β-keto acids can be formed from 2,2,2-trichloroethyl esters and undergo regiospecific aldol reactions with aldehydes and consequent decarboxylation (Scheme 101).[372]

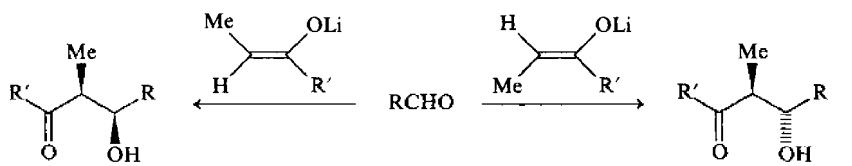
Silyl enol ethers undergo reaction with carbonyl compounds promoted by Lewis acids, but especially titanium tetrachloride. The reaction is thought to proceed *via* a titanium chelate which inhibits the reverse aldol process and the regiochemical integrity of the starting silyl enol ether is retained (Scheme 102).[373]



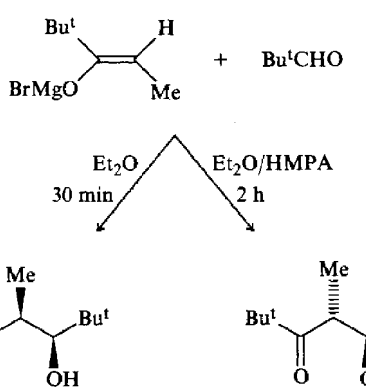
Scheme 96



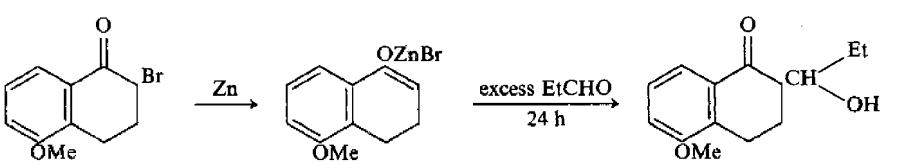
Scheme 97



Scheme 98

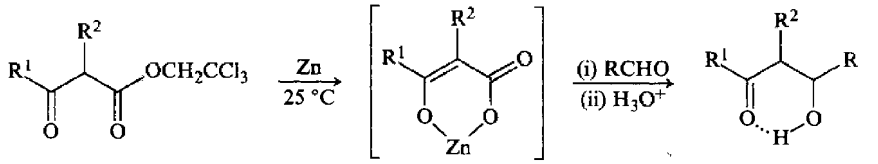


Scheme 99

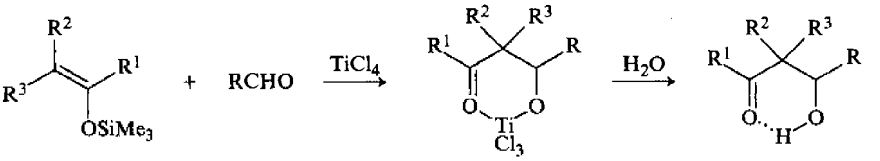


Scheme 100

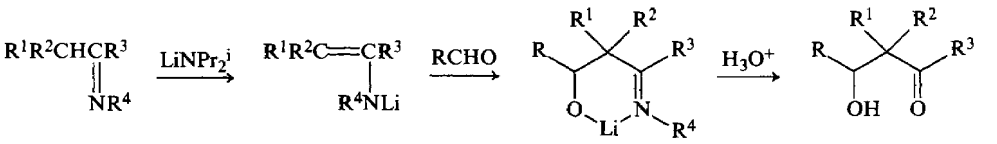
Lithium salts of ketone derivatives such as imines, oximes and hydrazones have also been used for directed aldol reactions (Scheme 103).[374,375] A recent example involves triple coordination of lithium in a very rigid transition state, to lead to regiospecificity in the product (Scheme 104).[376]



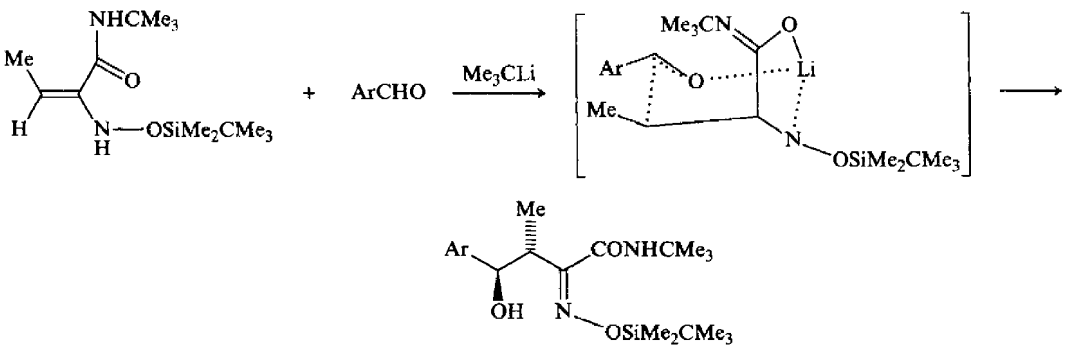
Scheme 101



Scheme 102

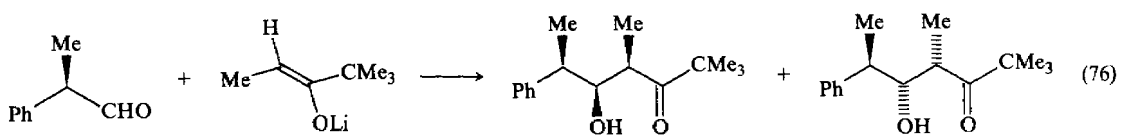


Scheme 103

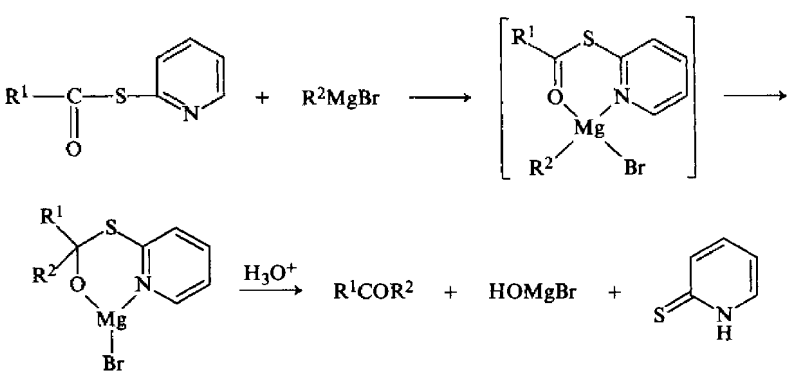


Scheme 104

Asymmetric induction is another important aspect of the directed aldol reaction. The approach involves the use of a chiral aldehyde which influences the stereochemistry of the addition reaction. Reaction of a chiral phenylpropanaldehyde with a lithium enolate yields only two of the possible diastereoisomers in the ratio of 86:14 (equation 76).[377]



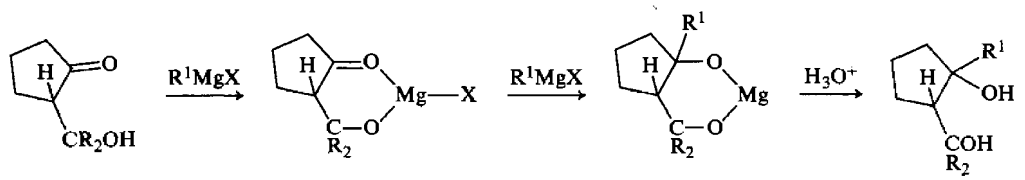
(76)



Scheme 105

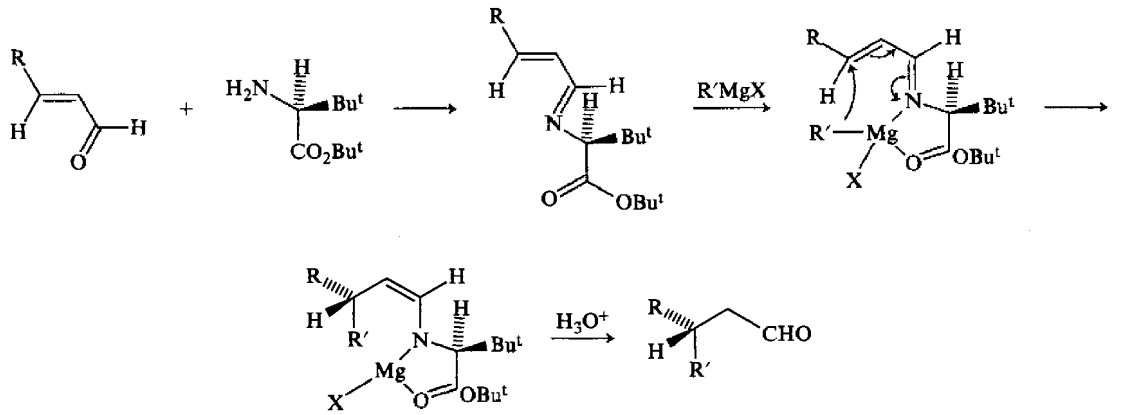
A different type of reaction, in which the intermediate formation of a chelate ring is crucial, is the reaction of pyridyl thioates with Grignard reagents, which achieves an overall conversion of an alkyl or aryl halide to a ketone (Scheme 105).[378] Grignard reactions are highly susceptible to chelation factors and stereoselectivity is observed in the addition of organomagnesium or

organolithium reagents to carbonyl compounds containing a coordinating group at an adjacent chiral centre. This is illustrated for a β-hydroxycyclopentanone, where the initially formed chelate is attacked by the Grignard reagent from the less hindered side so that the chelate ring can remain intact (Scheme 106).[379]



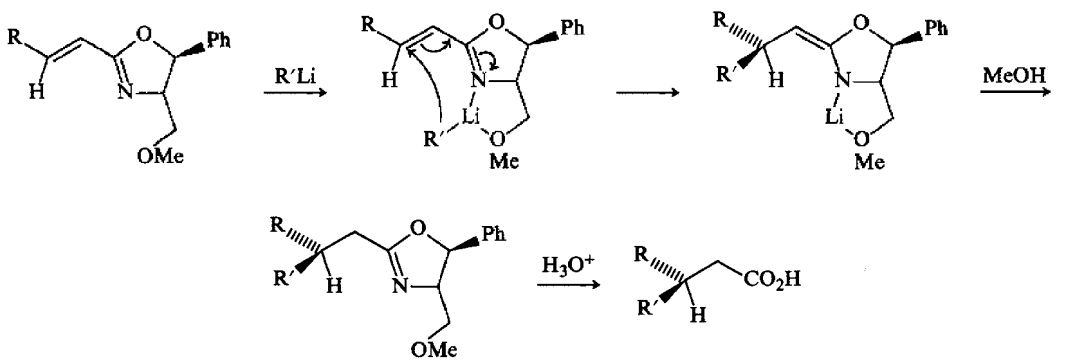
Scheme 106

The asymmetric addition of organomagnesium and organolithium reagents to α,β-unsaturated carbonyl compounds and especially imines can be achieved in situations where rigid chelation controls the geometry of the transition state. Stereospecific alkyl addition occurs in the case of a chiral leucine-derived imine to provide overall asymmetric alkyl addition to an α,β-unsaturated aldehyde (Scheme 107).[380,381]



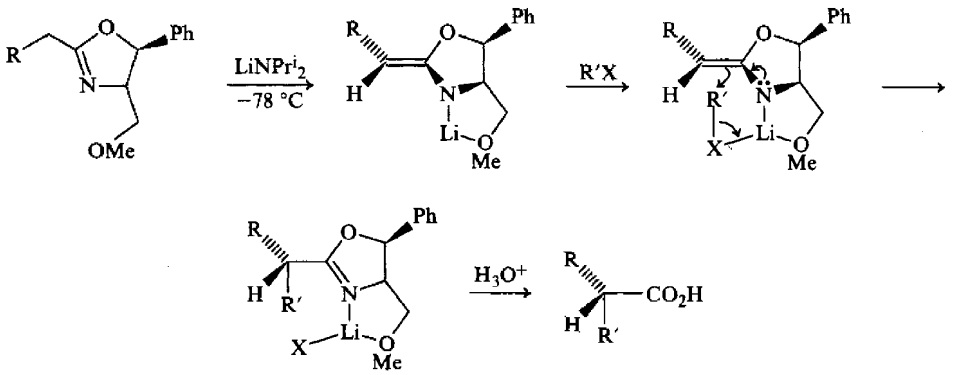
Scheme 107

A similar asymmetric addition occurs in the case of chiral α,β-unsaturated oxazolines, and yields chiral dialkylpropanoic acids after hydrolysis (Scheme 108).[382–384] A different type of reaction of chiral oxazolines leads to both chiral dialkylpropanoic acids and chiral dialkylacetic acids. In this case the chelated lithium oxazoline derivative is alkylated stereospecifically, as a consequence of the metalloenamine reactivity and the chelate geometry.

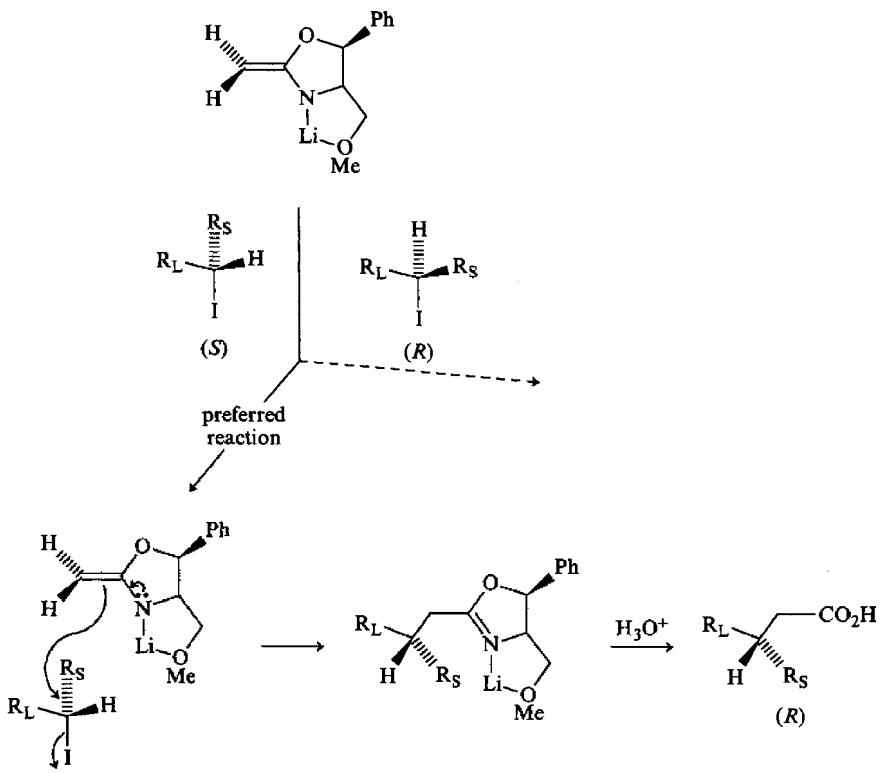


Scheme 108

Simple alkylation of the chiral chelate complex leads to formation of chiral dialkylacetic acids (Scheme 109).[385–388] Simpler chiral enamines can also be used. The formation of chiral propanoic acids results from a resolution of racemic alkyl halides by the interaction of a chiral lithiooxazoline, which recognizes and reacts with one enantiomer at the expense of the other (Scheme 110).[389] The above aspects of the asymmetric carbon–carbon bond formation from chiral oxazolines have been reviewed by Meyers.[390]



Scheme 109



Scheme 110

The importance of metal chelation in asymmetric syntheses involving carbonyl compounds has now been well recognized and this area of research is developing rapidly.

61.1.5 REFERENCES

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61.2

Catalytic Activation of Small Molecules

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61.2.1 INTRODUCTION

In commencing a discussion of coordination chemistry aspects of catalysis, it is well to look more closely at what is meant by the term 'catalyst' in relation to homogeneous catalysis. In general the word catalyst is applied to that complex which is added to the reaction mixture. Our current knowledge of the mechanisms of such reactions tells us that this complex rarely, if ever, takes part in the operating catalytic cycle which converts substrate to product. This complex is therefore much better termed the 'catalyst precursor'.

The mechanism of a homogeneously catalyzed reaction, again in the sense of that part of the chemistry occurring in solution which converts substrate to product, involves a series of highly reactive metal complexes any one of which has as much right as any other to be called the catalyst, and it is therefore more correct to speak of a 'catalytic cycle' or 'catalyst system' than of a catalyst. Since the term catalyst will doubtless remain in use for homogeneous systems, the above should be borne in mind when dealing with the literature.

A prime requirement for catalytic activity is that the species present in solution should be coordinatively unsaturated, permitting the reactants to form bonds to the metal ion. The following sections exhibit various ways of achieving this, which are summarized here. One is an increase in coordination number of the metal ion during the catalytic cycle, as exemplified by the conversion of four-coordinate d^8 to six-coordinate d^6 species. Another involves the spontaneous dissociation of a ligand from the complex. In a third manner, the removal of ligand(s) from the coordination sphere may be deliberately induced. Two common examples of this are hydrogenation of a coordinated alkene and protonation of a carboxylate group. Oxidation of a ligand to a non- or more weakly coordinating species (*e.g.* phosphine → phosphine oxide) and photodissociation have also been used. The latter possesses the disadvantage that recoordination may occur if irradiation is discontinued.

An important property of transition metal complexes is their ability to coordinate groups in a specific manner, leading to high regio- and stereo-specificity in the ensuing catalytic reaction. This has generally been described as the 'template effect'. Coordination to the transition metal can also lead to activation of the molecule for the reaction in question. This effect may vary from the cleavage of an existing bond in the molecule, as occurs in the activation of hydrogen, to a mere redistribution of electron density, as occurs on coordination of carbon monoxide or ethylene. Coordinative unsaturation, the template effect and substrate activation are basic to all reactions homogeneously catalyzed by transition metal complexes.

In the following sections a number of general types of reactions recur constantly. These are summarized here. The first three most commonly involve activation of the hydrogen molecule.

Heterolytic cleavage. This leads to formation of a metal hydride with release of a proton (equation 1). The formal oxidation state of the metal does not change. This mode of hydrogen activation is common in hydrogenation by complexes of ruthenium(II).

$$M + H_2 \rightarrow M{-}H + H^+ \tag{1}$$

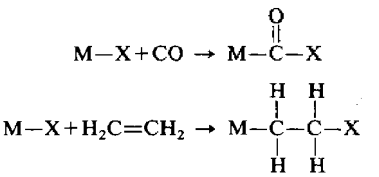
Homolytic cleavage. There are two versions of this process. The most important is oxidative addition (below). Rhodium(I) complexes exemplify this reaction. A *cis*-dihydride is formed with an increase of two in the formal oxidation state of the metal. The second form of homolytic cleavage involves two metal centres (equation 2). This is common for cobalt complexes.

$$2M + H_2 \rightarrow 2M{-}H \tag{2}$$

Oxidative addition. This reaction is quite general and normally involves the cleavage of a bond in the substrate and an increase of two in the formal oxidation state of the metal (equation 3). The most common example in catalysis is the oxidative addition of hydrogen.

$$M^{n+} + X{-}Y \rightarrow \begin{matrix} X \\ \diagdown \\ M^{(n+2)+} \\ \diagup \\ Y \end{matrix} \tag{3}$$

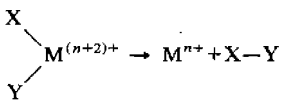
Insertion. The insertion reaction is one of the most important ways in which new bonds between the reactants are created by the catalyst. Two common forms of this reaction are illustrated by the insertion of carbon monoxide (equation 4) and ethylene (equation 5). The ligand X here may be generally described as a coordinated nucleophile. Insertion reactions are common to very many catalytic reactions.



(4)

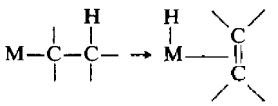
(5)

Elimination. Two kinds of elimination reaction are important in homogeneous catalysis. A catalytic cycle which has involved an oxidative addition generally ends with the reverse process of reductive elimination (equation 6). Rhodium-catalyzed hydrogenations end with this step.



(6)

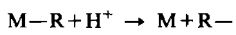
The other common elimination is the β-elimination (equation 7). This is a vital step in many palladium-catalyzed reactions, such as alkene arylation, and occurs as a side reaction leading to isomerization in other alkene reactions such as hydrogenation and hydroformylation.



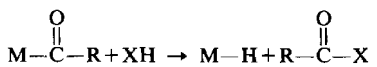
(7)

Protonation. Electrophilic attack of a proton on a metal-ligand bond is another terminating step in catalytic cycles (equation 8). This is typical of ruthenium-catalyzed hydrogenation.

Nucleophilic attack. Many carbonylation reactions are terminated by nucleophilic attack at a metal acyl (equation 9).

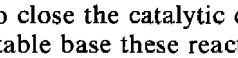


(8)



(9)

Proton loss. The extraction by base of a proton from a metal hydride leads to two-electron reduction of the metal (equation 10). In many palladium-catalyzed reactions, this step occurs after product formation and serves to close the catalytic cycle by regenerating the reduced form of the metal. In the absence of a suitable base these reactions become merely stoichiometric.



(10)

In the following sections many examples of these reactions occur in all manner of complexes. This article concentrates on the coordination chemistry and only the necessary minimum of information is supplied on details of catalyst performance. For rates, yields, selectivities, *etc.*, the original literature should be consulted. Small molecules are here defined as those having less than four non-hydrogen atoms.

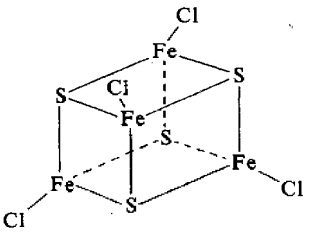
The oligomerization, cooligomerization and metathesis of small alkenes and alkynes and much of cobalt-catalyzed hydroformylation fall within the scope of the companion work 'Comprehensive Organometallic Chemistry' and are not dealt with here.

61.2.2 HYDROGENATION

61.2.2.1 Iron and Ruthenium

Complexes of iron have found only limited use as hydrogenation catalysts. The complex $[Fe_3(CO)_{10}NSiMe_3]$ loses one CO ligand on photolysis under H_2 to give the dihydride $[Fe_3(H)_2(CO)_9NSiMe_3]$. This effects the photocatalytic hydrogenation of methyl acrylate, 2,3-dimethylbutadiene, cyclobutene and cyclobutene dicarboxylate derivatives.[1] Replacement of one CO by a phosphine ligand leads to a catalytically inactive species. The triphenylphosphine complex *cis*-$[Fe(H)_2(CO)_2(PPh_3)_2]$ has been reported as a hydrogenation catalyst for dienes, but it undergoes extensive decomposition and a detailed investigation was not carried out.[2]

The iron–sulfur cluster (**1**), after treatment with phenyllithium in ether, was found to hydrogenate 1-octene and *trans*-2-, -3- and -4-octene with little or no apparent isomerization of the double bond.[3] The selectivity was dependent on the amount of phenyllithium used and the solvent.

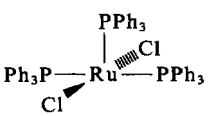


(**1**)

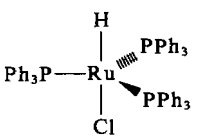
Wilkinson and co-workers have shown that $[RuCl_2(PPh_3)_3]$ (**2**) and complexes derived from it play key roles in ruthenium-catalyzed hydrogenation. The complex has a square pyramidal structure, the sixth position of the corresponding octahedron being occupied by a hydrogen atom of one of the phenyl rings. It reacts with hydrogen in presence of a base such as Et_3N according to equation (11).[4]

$$[RuCl_2(PPh_3)_3]+H_2+Et_3N \rightarrow [RuH(Cl)(PPh_3)_3]+Et_3NH^+\,Cl^- \qquad (11)$$

Complex (**3**) may be regarded as an immediate precursor of the species taking part in the catalytic cycle. If (**2**) is used as catalyst precursor, induction periods are observed during which (**3**) is formed by hydrogenolysis. The induction period may be prolonged if no base is present to neutralize the HCl formed. The use of a polar solvent instead of a base also promotes the hydrogenolysis.[4]



(**2**)

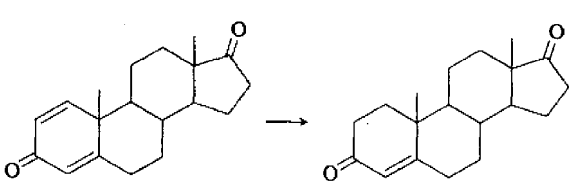


(**3**)

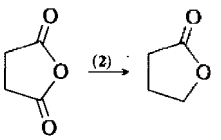
Aluminum alkyls have been shown to effect a rate enhancement in alkene hydrogenation by (**2**) and this was also attributed to promotion of the formation of hydridochloro complexes rather than to any participation of aluminum in the catalytic cycle.[5]

Compounds (**2**) and (**3**) show a marked preference for the hydrogenation of terminal double bonds relative to internal ones.[4] Compound (**2**) in presence of Et_3N has been used for the selective hydrogenation of 1,5,9-cyclododecatriene and 1,5-cyclooctadiene to the monoenes.[6] The former hydrogenation is important in connection with the synthesis of Nylon-12. The carbon–carbon double bond of activated alkenes is selectively hydrogenated by (**2**) or (**3**),[7,8] and (**2**) was found to lead to more active catalysts than the carbonyl complexes $[RuCl_2(CO)_2(PCy_3)_2]$, $[RuH(Cl)(CO)(PPh_3)_3]$, $[RuCl_2(CO)_2(PPh_3)_2]$ and, to a lesser extent, $[Ru(O_2CCF_3)_2(CO)_2(PPh_3)_2]$.[8]

A selective hydrogenation of 1,4-androstadiene-3,17-dione to 4-androstene-3,17-dione can be achieved with complex (**2**). The rate of hydrogenation is dependent on both the base added to promote equation (11) and on *para* substituents in the phosphorus ligand. Thus for the bases, the sequence was found to be $Et_3N \approx Et_2NH > PhNH_2 > BuNH_2$, with pyridine inhibiting the reaction. The effect of substituents in the phosphine was MeO > Me > H > F[9]. The further hydrogenation of (**4**) to the saturated diketone was suppressed relative to the formation of (**4**) by increasing the hydrogen pressure.[10] With temperature and hydrogen pressure both elevated, complex (**2**) efficiently hydrogenates both aldehydes[11] and ketones[12] to alcohols. Under similar conditions, the reduction of anhydrides to lactones has been reported (equation 13).[13]



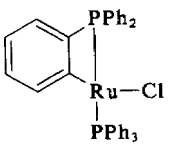
(**4**) (12)



(13)

The hydrogenation of both aliphatic and aromatic nitro compounds to the corresponding amines with (**2**) is also known.[14–16] In the hydrogenation of sugars, the presence of HCl was found necessary to prevent the decarbonylation of aldehyde groups to give $[RuH(Cl)(CO)(PPh_3)_3]$, which is inactive.[17] In almost all the above studies, complex (**2**) was used as catalyst precursor. It possesses the advantage of being air-stable, whereas (**3**) is not.[4]

Dinuclear complexes of the type $[RuH(X)L_2]_2$ (X = Cl, Br; L = PPh_3, $AsPh_3$) are reported to hydrogenate the C=C bond of acrylamide.[18] The stoichiometric reaction of (**3**) with an alkene leads to the *ortho*-metallated complex (**5**).[19]



(**5**)

This reaction is much too slow to play any role in catalytic hydrogenation. In the presence of D_2, the *ortho* positions of the phenyl rings are deuterated.[4] H-D exchange between H_2 and D_2 and between D_2 and solvent ethanol is also catalyzed by (**2**) and (**3**).[20]

Although certain points relating to the hydrogenation remain unclear, Scheme 1 gives the generally accepted mechanism.[4,21]

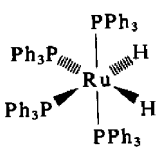
$$[RuH(Cl)(PPh_3)_3] + RCH{=}CH_2 \rightarrow \left[\begin{matrix} CH_2 \\ \| \\ CHR \end{matrix}\!\!-\!\!RuH(Cl)(PPh_3)_2\right] + PPh_3 \qquad (14)$$

$$\left[\begin{matrix} CH_2 \\ \| \\ CHR \end{matrix}\!\!-\!\!RuH(Cl)(PPh_3)_2\right] \rightarrow [Ru(CH_2CH_2R)Cl(PPh_3)_2] \qquad (15)$$

$$[Ru(CH_2CH_2R)Cl(PPh_3)_2] + H_2 + PPh_3 \rightarrow [RuH(Cl)(PPh_3)_3] + REt \qquad (16)$$

Scheme 1

The *cis*-dihydride complex $[Ru(H)_2(PPh_3)_4]$ (**6**) reacts with one mole of alkene to give a stoichiometric hydrogenation and it catalyzes the hydrogenation of terminal alkenes. The ruthenium(0) species $[Ru(PPh_3)_3]$ is thought to be formed. This then reacts with alkene or hydrogen depending on the conditions. The hydrogen activation step involves oxidative addition to $[Ru(PPh_3)_3]$ or its alkene complex instead of the heterolytic cleavage seen with ruthenium(II) species.[22] The nitrosyl complexes $[RuH(NO)L_3]$ (L = PPh_3, PPh_2Pr^i, $PPh_2C_6H_{11}$) are reported to catalyze the hydrogenation of styrene.[23] $[RuH(Cl)(\eta^6\text{-}C_6Me_6)PPh_3]$ hydrogenates monoenes, dienes, phenylacetylene and benzene.[24]

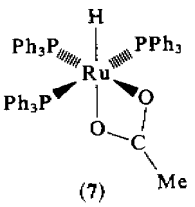


(**6**)

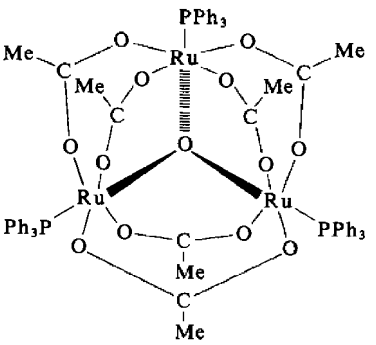
Treatment of $[RuH(Cl)(PPh_3)_3]$ (**3**) with potassium naphthalide at low temperature leads to the isolation of complexes formulated as $K^+[(PPh_3)_2Ph_2PC_6H_4Ru(H)_2]^-\cdot C_{10}H_8\cdot Et_2O$ and $K_2^+[(PPh_3)_3(PPh_2)Ru_2(H)_4]^{2-}\cdot 2C_6H_{14}O_3$. These species hydrogenate ketones, aldehydes and esters to alcohols, and nitriles to amines. Acrolein gave either propionaldehyde alone or a mixture with allyl alcohol.[25] The same complexes catalyze the partial hydrogenation of some polynuclear aromatic hydrocarbons, but isolated aromatic rings were not reduced.[26]

Wilkinson and his co-workers introduced another class of highly active hydrogenation catalysts in the form of the hydridocarboxylate complexes $[RuH(O_2CR)(PPh_3)_3]$ (R = Me, Et,

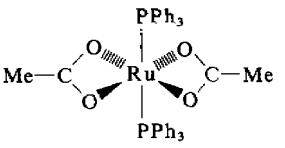
Pr^i, CF_3, C_6H_4, 2-OHC_6H_4). These complexes possess the advantage of being air-stable, unlike the hydridochloro analogue (**3**), and no base is needed, as with the dichloro complex (**2**).[27] In benzene, $[RuH(OAc)(PPh_3)_3]$ (**7**) shows the same marked selectivity for terminal alkenes as does (**3**). The mechanism of the hydrogenation is believed to be similar to that for complex (**3**). In methanolic solution, complex (**7**) is also active as a hydrogenation catalyst for terminal alkenes, and its activity is enhanced by the addition of a strong acid having a weakly coordinating anion, such as HBF_4.[28] Species showing similar catalytic properties in acidic methanol were obtained using $[Ru(H)_2(PPh_3)_4]$ or $[Ru(OAc)_2(PPh_3)_2]$ directly or by reduction of the trinuclear complex $[Ru_3O(OAc)_6(PPh_3)_3]$ (**8**)[29] in the presence of PPh_3 or by treating $[RuCl_2(PPh_3)_3]$ with $AgClO_4$. It appears that in all cases cationic methanol-solvated ruthenium(II)–triphenylphosphine complexes are formed. The catalytic activity was found to be dependent on the acid concentration.[28]



(7)



(8)



(9)

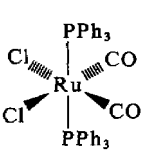
In a more detailed study of the hydrogenation using $[Ru(OAc)_2(PPh_3)_2]$ (**9**) in benzene, methanol and methanol containing *p*-toluenesulfonic acid, the rate passed through a maximum at low acid concentration. This was attributed to the stepwise protonation of the acetate ligands, leading to cationic, methanol-solvated complexes (equation 17).

$$[Ru(OAc)_2(PPh_3)_2] \xrightarrow[MeOH]{H^+} [Ru(OAc)(PPh_3)_2(MeOH)_x]^+ \xrightarrow[MeOH]{H^+} [Ru(PPh_3)_2(MeOH)_y]^{2+} \quad (17)$$

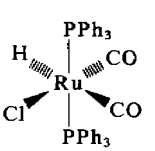
Benzene or methanol without acid gave much poorer rates. Similar behavior was observed with both conjugated and non-conjugated dienes and these could generally be hydrogenated to the monoenes with very high selectivity. The superior coordinating ability of the diene appears to be the cause of this.[30]

Using the sulfonated phosphine $PPh_2(m\text{-}C_6H_4SO_3H)$ (mSPPh$_2$) the complexes $[RuCl_2(m\text{SPPh}_2)_3]$, $[RuH(Cl)(m\text{SPPh}_2)_3]$ and $[RuH(OAc)(m\text{SPPh}_2)_3]$ have been prepared. These are water-soluble analogues of complexes (**2**), (**3**) and (**7**). In aqueous solution at normal pressure they hydrogenate both C=C and C=O bonds.[31] A kinetic investigation led to a mechanism analogous to that of Scheme 1 being postulated for the hydrogenation of crotonic and pyruvic acids.

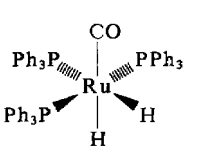
Carbonyl complexes of ruthenium have been mentioned briefly above. They are dealt with in detail here. $[RuCl_2(CO)_2(PPh_3)_2]$ (**10**) in dimethylacetamide has been shown to reduce the C=C bond of methyl vinyl ketone at 80 °C and normal pressure of hydrogen. Although 1-octene was not hydrogenated it was efficiently isomerized to 2-, 3- and 4-octene.[32] At higher temperature and pressure, 1,5,9-cyclododecatriene was hydrogenated with very good selectivity to cyclododecene with a turnover number (moles product formed/moles catalyst used) of 32 100.[33] Other ruthenium complexes were investigated but were less efficient. Rates of hydrogenation of a series of alkenes



(10)



(11)



(12)

with (**10**) were found to vary in the order conjugated dienes > non-conjugated dienes > terminal alkenes > internal alkenes.[34] The mechanism probably involves a hydrogenolysis step, as for $[RuCl_2(PPh_3)_3]$ (equation 18).

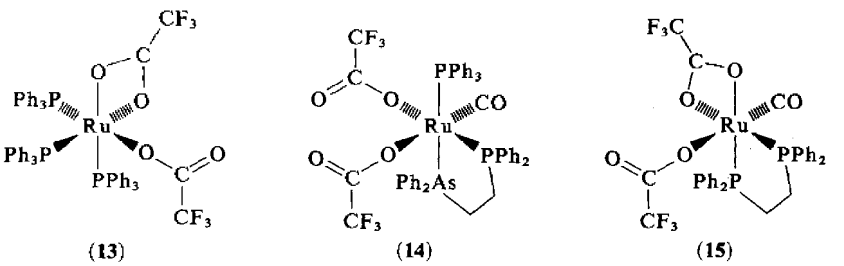
$$[RuCl_2(CO)_2(PPh_3)_2] + H_2 \rightarrow [RuH(Cl)(CO)_2(PPh_3)_2] + HCl \quad (18)$$

At 160–200 °C and 1.5 MPa hydrogen pressure, (**10**) is an efficient catalyst for the hydrogenation of simple aliphatic and aromatic aldehydes to alcohols, giving turnover numbers of 10 000–95 000.[35]

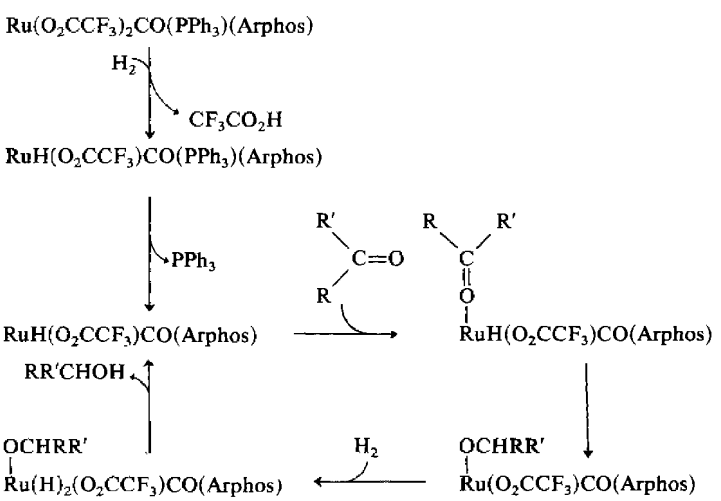
$[RuHCl(CO)(PPh_3)_3]$ (**11**) has been shown to reduce propionaldehyde, heptaldehyde, benzaldehyde and acetone to alcohols. The hydrogen pressure used here was significantly higher than in the above studies. $[RuCl_2(PPh_3)_3]$ and $[RuH(Cl)(PPh_3)_3]$ were also about as effective as (**11**), but $[Ru(CO)_3(PPh_3)_2]$ was less so.[36] In a further study, acetone and other ketones were reduced to alcohols by the four complexes above and by $[RuH(NO)(PPh_3)_3]$, $[RuCl_2(CO)_2(PPh_3)_2]$, $[Ru(H)_2(CO)(PPh_3)_3]$ (**12**), $[Ru(H)_4(PPh_3)_3]$ and $[Ru(H)_2(PPh_3)_4]$ (**6**). The best results were obtained with complex (**11**), the nitrosyl complex and the dichloride (**10**). The addition of water to these reactions was found to be beneficial in most cases.[37]

Use of the same complexes to catalyze the hydrogenation of propionaldehyde showed that $[RuH(Cl)(PPh_3)_3]$ (**3**) was the most effective. However, complex (**11**) was preferred for general use because of its stability in air.[38] Turnover numbers up to 32 000 were achieved. Complex (**11**) decomposed during the reactions to give a variety of species which could not be characterized.

The hydrogenation of heptanal and cyclohexanone is also catalyzed by the complexes $[Ru(O_2CCF_3)_2(CO)(PPh_3)_2]$ (**13**), $[Ru(O_2CCF_3)_2(CO)(PPh_3)(Ph_2PCH_2CH_2AsPh_2)]$ (**14**) and $[Ru(O_2CCF_3)_2(CO)(Ph_2PCH_2CH_2CH_2PPh_2)]$ (**15**). Complex (**13**) formed a significant amount of the dicarbonyl $[Ru(O_2CCF_3)_2(CO)_2(PPh_3)_2]$ during the reaction, whereas with (**14**) no other complex could be detected. Complex (**15**) was the most active catalyst and, here again, a number of uncharacterized complexes were formed.[39] The proposed mechanism for the hydrogenation is shown in Scheme 2. These complexes also catalyze the dehydrogenation of alcohols.



(**13**) (**14**) (**15**)



Scheme 2

In addition to reducing C=O bonds, the dihydride (**12**) also hydrogenates 1-hexene.[2] At normal pressure and 45 °C (**12**) acts principally as an isomerization catalyst. At 1.7 MPa, hexane is formed but 2-hexene remains the major product.

The ruthenium hydrogenation catalysts described above all contain phosphorus ligands. Some phosphorus-free catalytic systems have been reported. Thus the oxygen-centred trinuclear acetate $[Ru_3O(O_2CMe)_6(H_2O)_3]^+$ (**16**), whose structure is analogous to (**8**), hydrogenates alkenes in DMF solution at normal pressure of hydrogen and 80 °C.[40] The catalysis shows a number of unusual features. Thus internal alkenes are hydrogenated more rapidly than terminal ones. The rate order is cyclic alkene > internal alkene > terminal alkene. Terminal alkynes are reduced even more

slowly. The phosphine complexes of ruthenium generally show a marked preference for terminal alkenes. In hydrogenations with (**16**) it was also noted that no isomerization products could be detected. The reactions are generally autocatalytic. $[HRu_3O(O_2CMe)_5]^+$ is thought to be first formed, followed by $[Ru_3O(O_2CMe)_4]^+$, both of which are solvated by DMF. The latter complex is responsible for the bulk of the hydrogenation, which involves only one ruthenium atom in the complex. Activation of hydrogenation precedes alkene coordination.

Chloro complexes of ruthenium(II) were found to hydrogenate maleic and fumaric acids to succinic acid slowly at 60–80 °C and normal pressure of hydrogen. Non-activated alkenes lead to the production of ruthenium metal. The structures of the species involved are unknown. The mechanism involves coordination of the alkene followed by heterolytic cleavage of hydrogen, giving a ruthenium(II) hydride as the second step.[41]

In *N,N*-dimethylacetamide solution the reduction by hydrogen of ruthenium(III) chloride is claimed to produce ruthenium(I) complexes which hydrogenate ethylene, maleic and fumaric acids. The complexes are thought to be dimeric but their precise structures are unknown. Interestingly, these d^7 ruthenium(I) complexes are believed to activate hydrogen by oxidative addition whereas heterolytic cleavage of hydrogen occurs with most ruthenium catalysts (equation 19).

$$Ru^{I} + H_2 \rightarrow Ru^{III}(H)_2 \tag{19}$$

Hydrogen activation precedes the coordination of the alkene. Reviews on hydrogen activation in relation to homogeneous catalysis are available.[43,44] General reviews on homogeneous hydrogenation are listed at the end of Section 61.2.2.

61.2.2.2 Cobalt

The pentacyanocobaltate(II) ion has long been known to catalyze alkene hydrogenation, mainly of conjugated dienes. A review of the early work is available.[45] The catalyst system shows negligible activity for the hydrogenation of non-activated monoenes. A major disadvantage is that the system is inhibited by excess substrate, and the turnover numbers obtained are generally less than 2.

The activity and selectivity observed in these systems are markedly solvent dependent. In water alone, deactivation eventually occurs. This has led to the use of mixtures of water and organic solvents, or to polar organic solvents alone. For hydrogenation studies the catalyst is generally prepared *in situ* by mixing the appropriate quantities of a cobalt salt and a Group I cyanide. The resulting green solution is generally considered to contain the ion $[Co(CN)_5]^{3-}$, but it has been pointed out that the colour is more probably due to the presence of $[Co(CN)_5H_2O]^{3-}$.[46]

In the hydrogenation of cyclopentadiene to cyclopentene it was found that ethanolic solutions retained their catalytic activity for months, whereas aqueous solutions rapidly lost their activity. Fresh solutions in either solvent gave similar initial rates.[47] The product of the hydrogenation is dependent on both the solvent and the CN/Co ratio. In the hydrogenation of butadiene in aqueous solution the major product was *trans*-2-butene at CN/Co = 5.1 and 1-butene at CN/Co > 5.1. The total concentration also affects the product distribution. In glycerol–methanol solution similar results were observed, the change occurring at CN/Co = 5.4. In ethylene glycol–methanol solution the production of *cis*-2-butene was favoured.[48]

The hydrogenation of *trans*-1-phenyl-1,3-butadiene has been discussed[49] in terms of the mechanism originally proposed,[45] and η^3-allyl species were invoked. NMR studies on the hydrogenation of butadiene have shown that η^1-but-2-enyl and η^3-1-methylallyl complexes are present in the reaction mixture. With isoprene, an η^1-methylbut-2-enyl complex was observed.[50] By using a two-phase system and a phase-transfer catalyst, the turnover numbers attainable with conjugated dienes can be increased to about 30.[51]

In addition to conjugated dienes, cyanocobalt catalysts also hydrogenate the C=C bond of activated alkenes.[52] Carvene, mesityl oxide, 2-cyclohexenone, benzalacetone and an androstenone derivative were reduced in this way.[53]

Hydrogenations with $[Co(CN)_5]^{3-}$ as catalyst have been long thought to involve radical reactions. Hydrogen is activated prior to reaction with the alkene, the mechanism involving homolytic fission by two $[Co(CN)_5]^{3-}$ ions (Scheme 3).[54]

The transfer of hydrogen to the alkene also occurs by a radical process,[55,56] and not by the insertion reaction which is much more common in homogeneous hydrogenation. These kinetic studies were carried out using cinnamic acid as alkene. The observation of alkenyl and allyl species in diene hydrogenation suggests that a different mechanism of hydrogen transfer may

$$[Co(CN)_5]^{3-} + H_2 \rightarrow [CoH(CN)_5]^{3-} + H\cdot \quad (20)$$

$$[Co(CN)_5]^{3-} + H\cdot \rightarrow [CoH(CN)_5]^{3-} \quad (21)$$

$$[CoH(CN)_5]^{3-} + X \rightarrow [Co(CN)_5]^{3-} + HX\cdot \quad (22)$$

$$[CoH(CN)_5]^{3-} + HX\cdot \rightarrow [Co(CN)_5]^{3-} + H_2X \quad (23)$$

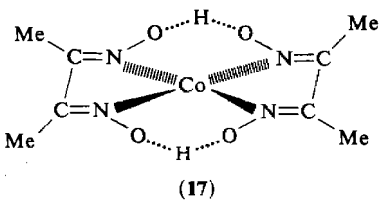
(X = conjugated diene, activated alkene)

Scheme 3

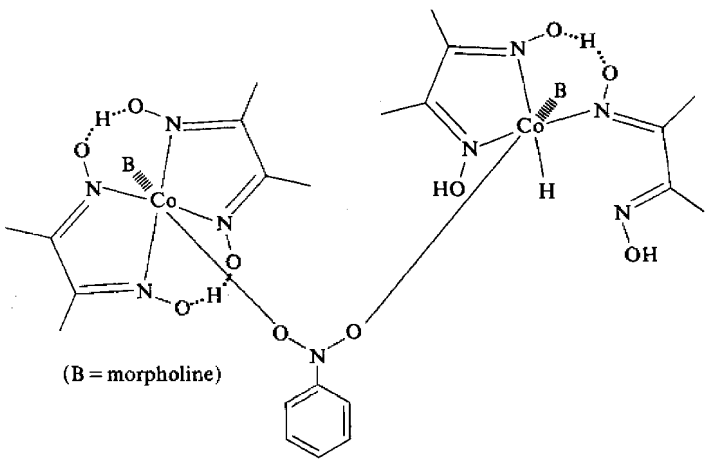
operate there, as these reactions appear slow enough for intermediates to be observed directly by NMR.

Modification of the $[Co(CN)_5]^{3-}$ catalyst by addition of diamines has been reported to lead to higher catalytic activity in diene hydrogenation and a predominant 1,2-addition of hydrogen. Such systems are thought to contain the species $[CoH(CN)_3(diamine)]^-$. Ethylenediamine, 2,2′-bipyridyl and 1,10-phenanthroline were the diamines used.[57,58]

Bis(dimethylglyoximato)cobalt(II) (**17**), generally in the presence of a base such as pyridine, has been studied as a potential analogue of the cobalt-containing vitamin B_{12}. The base coordinates in the axial position, giving a square pyramidal structure. These complexes reduce the C=C bond of activated alkenes at normal temperature and hydrogen pressure.[59] As with the $[Co(CN)_5]^{3-}$ system, the attainable turnover numbers are very limited. With methyl methacrylate the pyridine adduct of (**17**) gave a turnover number of 10. The hydrogenations are generally carried out in alkaline media and there appears to be an optimum basicity for a given alkene.[60] The active species is thought to be $[CoH(DMG)_2(base)]$ or $[Co(DMGH)_2(base)]^-$, where $[Co(DMGH)_2]$ represents complex (**17**).



(**17**)

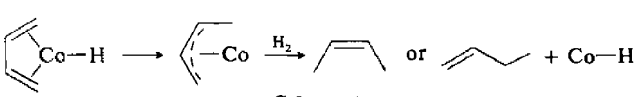


(**18**)

In presence of morpholine, (**17**) catalyzes the hydrogenation of nitrobenzene to aniline.[61] A near twofold excess of the amine relative to (**17**) was used. At a higher excess, catalysis ceased. This was attributed to formation of a bis-morpholine complex. The hydrogenation proceeds best in solvents such as acetone, ethyl acetate or THF.[62] The transfer of the first hydrogen atom to nitrobenzene was found to be rate determining and a dinuclear nitrobenzene complex (**18**) was postulated. The base (**B**) is morpholine.

In presence of pyridine, (**17**) catalyzes the reduction of activated alkenes by both hydrogen and $NaBH_4$. Vitamin B_{12} also catalyzed these reactions.[63]

Reduction of a cobalt(II) halide in presence of 2,2′-bipyridyl with zinc in THF–ethanol leads to cobalt(I)–bipyridyl complexes which hydrogenate butadiene to *cis*-2-butene at 25 °C and normal pressure of hydrogen. For different halides the rate decreases in the order I > Br > Cl. 1,10-Phenanthroline complexes were also active.[64] Here again, the catalyst does not tolerate an excess of diene. The proposed mechanism for the hydrogenation is given in Scheme 4.



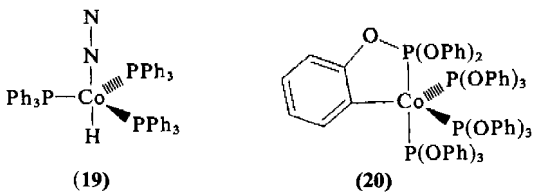
Scheme 4

The triphenylphosphine complexes $[CoX(PPh_3)_3]$ (X = Cl, Br, I) exhibit fairly high selectivity in the hydrogenation of dienes. Internal double bonds were reduced preferentially. The addition

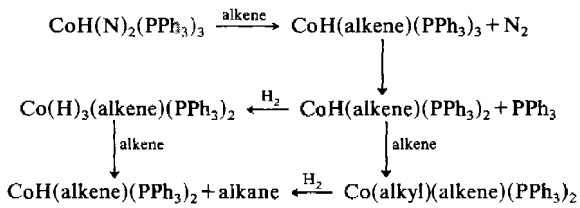
of a Lewis acid to activate the complexes was necessary. The activation is thought to involve the removal of the halide ligand and formation of a diene complex (equation 24).[65]

$$[CoBr(PPh_3)_3] + \text{diene} + BF_3{\cdot}OEt_2 \rightarrow [Co(\text{diene})(PPh_3)_3]^+ [BF_3Br]^- + Et_2O \quad (24)$$

The complex $[CoH(N_2)(PPh_3)_3]$ (**19**) in presence of sodium naphthalide gave a paramagnetic species which hydrogenates styrene at normal temperature and hydrogen pressure.[66] The kinetics of the hydrogenation of cyclohexene by (**19**) were studied and the mechanism given in Scheme 5 was deduced, in which two alternative routes were considered. It was not possible to distinguish between them on the basis of the kinetic evidence.[67]



(**19**) (**20**)

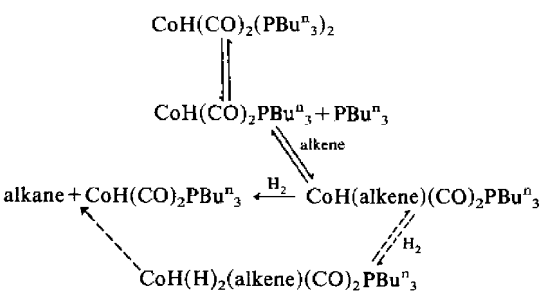


Scheme 5

In a further kinetic study on the hydrogenation of cyclohexene, $[Co(H)_3(PPh_3)_3]$ was used as catalyst.[68] The mechanism is thought to involve dissociation of a PPh_3 ligand to permit alkene coordination. The hydrogenation leads to a cobalt(I) species formulated as $[CoH(PPh_2)_2]$, probably solvated, which then oxidatively adds hydrogen to regenerate the trihydride.

$[CoH(BH_4)(PCy_3)_2]$ in benzene solution hydrogenates terminal alkenes and styrene faster than internal alkenes or dienes. Isomerization of terminal alkenes caused a rapid deterioration of the reaction rate.[69] An *ortho*-metallated triphenyl phosphite complex, for which the structure (**20**) was proposed, gave a turnover number of more than 300 in the hydrogenation of 1-butene. Isomerization was not observed in this case.[70]

Phosphinecarbonyl complexes of cobalt have long been known to act as hydrogenation catalysts. In a recent study involving cyclohexene the kinetics of its hydrogenation by the complex $[CoH(CO)_2(PBu^n_3)_2]$ were studied. Unlike the systems described above, the carbonyl complexes generally require elevated temperature and pressure. The proposed mechanism is given in Scheme 6.



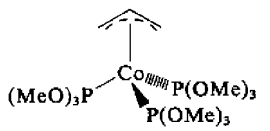
Scheme 6

In many studies, $[Co_2(CO)_8]$ was treated *in situ* with phosphorus ligands to obtain the catalytic species. Such systems lie outside the scope of this work and the companion volumes 'Comprehensive Organometallic Chemistry' should be consulted.

Cobalt catalysts have been shown to hydrogenate arenes to saturated hydrocarbons. The $Co(acac)_2$-$AlHBu^i_2$-PBu^n_3 system hydrogenates benzene to cyclohexene, but the presence of styrene was necessary, otherwise the reaction ceased. The styrene was also hydrogenated.[72]

Muetterties and co-workers have reported the hydrogenation of arenes catalyzed by $[Co\{P(OMe)_3\}_3(\eta^2\text{-}C_3H_5)]$ (**21**) at room temperature and normal pressure of hydrogen.[73] The

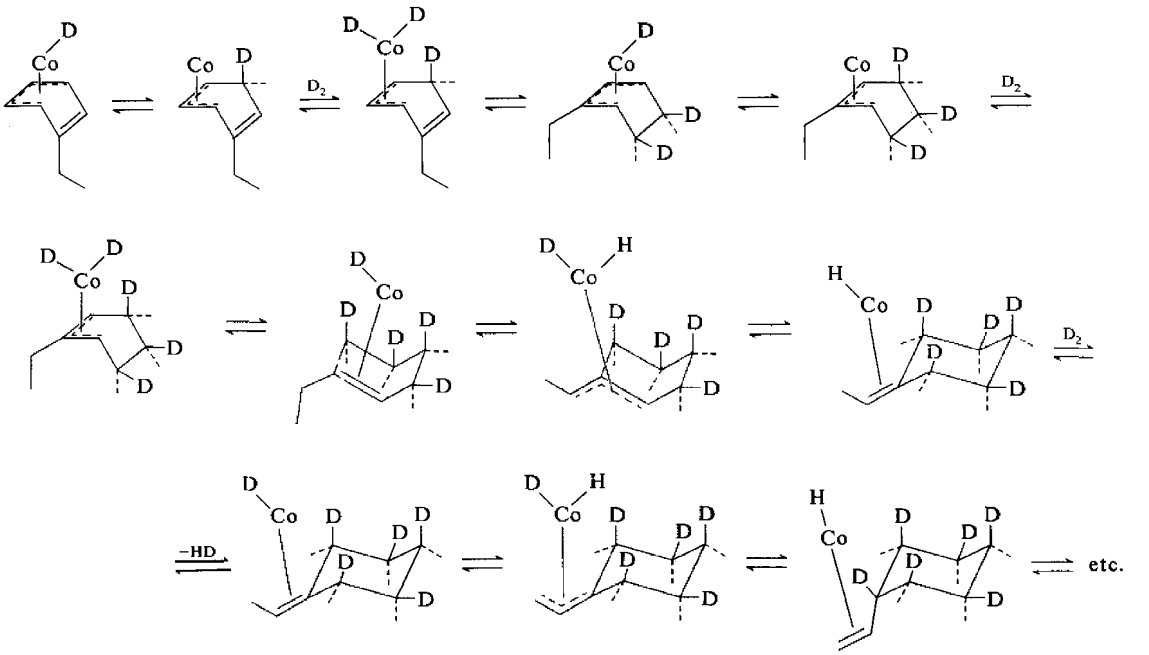
product of benzene hydrogenation was cyclohexane, no cyclohexadienes or cyclohexene being detected. Using deuterium, it was shown that *cis* addition of all three molecules of deuterium occurred. The low activity of the triphenyl phosphite complex could be raised considerably by using more bulky phosphites or phosphines, but the lifetime of the catalyst is reduced. Surprisingly, arenes were reduced at rates similar to those of alkenes, whereas most hydrogenation catalysts react far more rapidly with alkenes and benzene can often be used as a solvent for alkene hydrogenation.



(21)

The attainable turnover numbers lie in the range 20–40. Complex (**21**) hydrogenates many arenes and alkenes though the conversions are often low.[74] The crystal structure of the η^3-cyclooctenyl analogue $[Co\{P(OMe)_3\}_3(\eta^3\text{-}C_8H_{13})]$ (**22**) has been determined. Considering the η^3-unit as a single ligand, the molecule is pseudotetrahedral. This complex also catalyzes arene hydrogenation.[75]

Alkyl-substituted arenes undergo H/D exchange in the alkyl group during arene hydrogenation. The η^3-cyclooctenyl group of (**22**) was removed by hydrogenolysis early in the reactions and the coordinatively highly unsaturated hydride $[CoH\{P(OMe)_3\}_2]$ is thought to be involved.[76] Scheme 7 shows the proposed mechanism.



Scheme 7 Phosphite ligands omitted

61.2.2.3 Rhodium

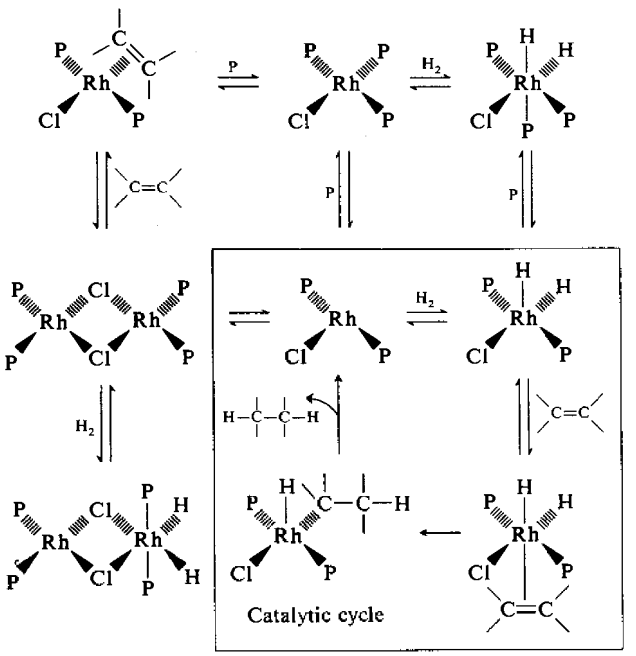
Homogeneous hydrogenation by rhodium complexes is perhaps the classic example occurring in catalysis of activation of the hydrogen molecule by oxidative addition to d^8 rhodium(I) complexes (equation 3). The relatively high H—H bond energy (450 kJ mol^{-1}) is believed to be overcome by the donation of electron density from a filled metal *d*-orbital to the empty σ^* antibonding orbital of the hydrogen molecule. Very often, this oxidative addition is highly reversible at normal temperature and hydrogen pressure and the equilibrium can be displaced to either side almost instantaneously by introducing or removing hydrogen.

The discovery of the complex $[RhCl(PPh_3)_3]$ (**23**), now known as Wilkinson's catalyst, represented a tremendous step forward in homogeneous hydrogenation.[77,78] It is a highly active catalyst for the hydrogenation of alkenes and, unlike the cobalt complexes, it remains active at high

alkene/catalyst ratios.[79] Its introduction led to greatly increased interest in both hydrogenation and homogeneous catalysis generally. The complex may be obtained as either red or orange crystals, the red form being the more common one. Both forms have a near square planar structure which is slightly distorted towards the tetrahedral. The distortion is somewhat more pronounced in the red form. There are close interactions between *ortho* hydrogen atoms of the phenyl groups and the metal, which are different in the two forms.[80]

In their original studies, Wilkinson and co-workers postulated a mechanism involving oxidative addition of hydrogen to rhodium(I) to give a rhodium(III) dihydride, followed by coordination of alkene. The precise nature of the hydrogen transfer to the alkene was not clear at that time, but the general outlines of the mechanism were correct.

There have been may inconclusive kinetic studies of the hydrogenation, but the detailed mechanism has now been elucidated by Halpern and his co-workers,[81–83] and is summarized in Scheme 8.



Scheme 8

The actual catalytic cycle is enclosed in the rectangle. The species outside this can also lead to hydrogenation, but at a much slower rate. The dissociation of one PPh_3 ligand forming $[RhCl(PPh_3)_2]$ leads into the catalytic cycle. Further ligand dissociation, not shown in Scheme 8, may occur. When the more strongly coordinating styrene is hydrogenated (Scheme 8 relates to cyclohexene), additional steps occurred in the reaction, involving the formation after hydrogenation of a bis-styrene complex $[Rh(H)_2Cl(PPh_3)(styrene)_2]$.[81] Halpern has discussed the difficulties involved in obtaining a reliable mechanistic understanding of such a complex system.[81]

In the 18 years since its discovery, Wilkinson's catalyst has been used to hydrogenate all kinds of unsaturated compounds and great efforts have been made to develop other phosphorus ligand-containing catalysts of both rhodium and other metals. This in turn has led to catalytically active complexes which do not contain phosphorus. In Table 1 the hydrogenation of various unsaturated compounds catalysed by $[RhCl(PPh_3)_3]$ is summarized. In some cases the addition of deuterium and tritium to the substrate was investigated.[84,95,101,102]

Osborn and co-workers introduced a series of cationic rhodium–diene complexes of the general type $[Rh(diene)_2(phosphine)_2]^+ X^-$ (X^- = non-coordinating anion).[103–106] Norbornadiene was the preferred diene, although 1,5-cyclooctadiene was also used. PPh_3, PPh_2Me, $PPhMe_2$ or a chelating diphosphine were generally the phosphorus ligands and the anions were typically ClO_4^- or PF_6^-. These complexes were shown to hydrogenate alkenes to alkanes,[104] dienes to monoenes[106] and alkynes to *cis*-alkenes.[105]

Complexes of this type in which chiral diphosphines are present have become most important in asymmetric catalytic hydrogenation (see Section 61.2.3). Under hydrogenation conditions the diene is reduced to give cationic solvated rhodium(I)–phosphine complexes which initiate the

Table 1 Applications of $[RhCl(PPh_3)_3]$ in the Catalytic Hydrogenation of Unsaturated Compounds

Substrates	*Ref.*
Ethylene, cyclohexene	5
Cycloalkenes	84
Alkenes, cycloalkenes	85
Methylenecyclohexene derivatives	86, 87
Allene	88
Terpenes	89
Triterpenoids	90
Perhydroaromatics, butadiene rubbers	91
Cyclohexenol derivatives	92
Cycloalkenes, activated alkenes	93
Alkenes, cycloalkenes, dienes, conjugated dienes, activated alkenes	94
Cyclohexene, unsaturated acids	95
Monoepoxybutadiene, phenylcyclopropane, styrene	96
Unsaturated thiophene derivatives	97
Nitroaromatics	98
Activated alkenes, nitrostyrene derivatives	99
Lipids	100

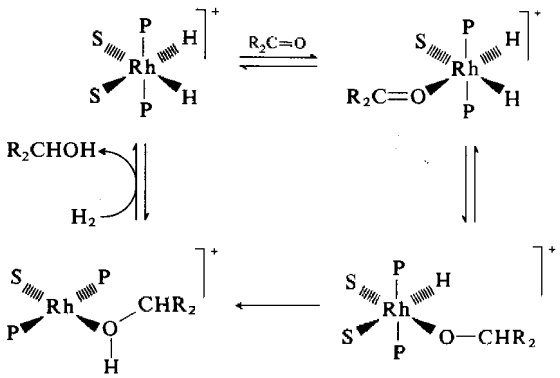
catalytic cycle. The triphenylphosphine complexes then activate hydrogen by oxidative addition to give $[Rh(H)_2(PPh_3)_2(solvent)_2]^+$, whereas with diphos as ligand, no reaction with hydrogen occurs in absence of alkene.[107] From solutions of the solvated species $[Rh(diphos)]_2^{2+}$ a dinuclear complex has been isolated, which reverts to the mononuclear complex on redissolving. Some other hydrogenations catalyzed by cationic rhodium complexes of this type are summarized in Table 2.

Table 2 Some Other Hydrogenations Catalyzed by Cationic Rhodium–Phosphine Complexes

Complexes	*Substrates*	*Ref.*
$[Rh(nbd)Ph_2P(CH_2)_nPPh_2]^+$ $n = 4, 5$	3-Phenylbut-3-en-2-ol, 4-phenylpent-4-en-2-ol	108
$[Rh(nbd)L_2]^+$ $L = PPhEt_2$, PBu^n_3, PMe_3	Unsaturated esters	109
$[Rh(cod)L_2]^+$ $L = PPh_2Me$, $PPhMe_2$	1-Hexene, cyclohexene, benzophenone	110
$[Rh(cod)(PCy_3)_2]^+$	Alkenes, cycloalkenes, ketones, cyclic ketones	111
$[Rh(nbd)(PEt_3)_2]^+$	Ketones	112
$[Rh(H)_2L_2(solvent)_2]^+$ $L = PPh_2Me$, $PPhMe_2$, PMe_3	Ketones, aldehydes	113
$[Rh(nbd)Pr^i_2P(CH_2)_2PPr^i_2]^+$	Ketones, aldehydes	114
$[Rh(nbd)(PEt_3)_2]^+$	Aldehydes	115
$[Rh(nbd)L_2]^+$ $L = PPh_3$, PEt_3, PMe_3, diphos	Styrene oxide	116
$[Rh(nbd)L_2]^+$ $L = PPh_3$, PEt_3, PMe_3, diphos	3,4-Epoxybut-1-ene	117

In addition to the hydrogenation of C—C multiple bonds, such cationic species have now been shown to reduce ketones, aldehydes and epoxides. The mechanism of hydrogenation of a C=O bond is believed to be analogous to that for alkenes, with the insertion step leading to an alkoxide complex (Scheme 9).[113]

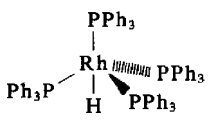
The implication of metal hydrides in homogeneous hydrogenation led to their direct use as catalyst precursors. $[RhH(PPh_3)_4]$ (**24**) was shown to hydrogenate 1-hexene with accompanying isomerization to 2-hexene. Dissociation of PPh_3 occurred to give coordinatively unsaturated species.[118] These underwent oxidative addition to give rhodium(III) trihydrides, this being the rate determining step. Alkene insertion and reductive elimination of hexane complete the catalytic cycle, regenerating a rhodium(I) monohydride. In the hydrogenation of ethylene with complex (**24**), however, it was believed that a rhodium(I)–ethyl complex was first formed, which then reacted with hydrogen.[119] In the presence of an equimolar amount of PEt_3, complex (**24**) effected



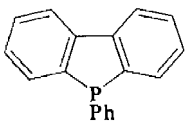
(P = phosphorus ligand, S = solvent)

Scheme 9

the hydrogenation of 1,3-dienes to 1-alkenes.[120] Another mixed phosphine catalyst which reduces terminal alkenes is $[RhH(PF_3)(PPh_3)_3]$.[121]



(24)



(25) DBP

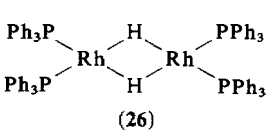
The catalyst system $[RhCl(nbd)]_2/PPh_3/Et_3N$ has been shown to hydrogenate ketones under mild conditions.[122] Many examples were given. The catalytic activity was again attributed to rhodium(I)-hydrido-phosphine complexes generated according to equation (25) after hydrogenation of the coordinated diene.

$$[Rh(H)_2Cl(PPh_3)_n] + Et_3N \rightleftharpoons [RhH(PPh_3)_n] + Et_3NH^+ Cl^- \qquad (25)$$

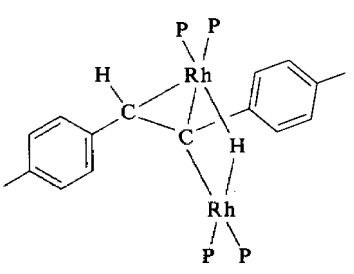
The 5-phenyldibenzophosphole (**25**) complex $[RhH(DBP)_4]$ catalyzes the hydrogenation of terminal alkenes, 1,5-hexadiene and some substituted alkenes. With 1-hexene it was far more active than $[RhCl(PPh_3)_3]$ or $[RhH(PPh_3)_4]$. The mechanism is again thought to involve dissociation of DBP followed by alkene insertion into the rhodium hydride bond and subsequent reaction with hydrogen.[123]

The hydrido complex $[RhH(PPr^i_3)_3]$ and $[Rh_2(N_2)\{P(C_6H_{11})_3\}_4]$ have been shown to hydrogenate nitriles to primary amines at normal temperature and pressure, with turnover numbers of up to 100 being attained.[124] This is a most interesting observation in view of the coordinating ability of primary amines, which might have been expected to saturate the coordination sphere of the rhodium, putting an end to catalysis.

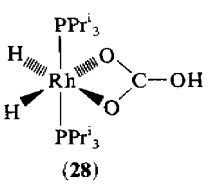
In the homogeneous hydrogenation of alkynes it has generally been found that *cis*-alkenes are formed exclusively in the hydrogenation step, any *trans*-alkene occurring being due to a subsequent isomerization. It has now been reported that $[Rh_2(H)_2\{P(OPr^i)_3\}_4]$ (**26**) converts alkynes directly to *trans*-alkenes.[125] The dinuclear unit is thought to remain intact during the catalytic cycle. From the reaction of (**26**) with di(*p*-tolyl)acetylene, a vinyl complex (**27**) was isolated in which the *trans*-alkene was present.



(26)



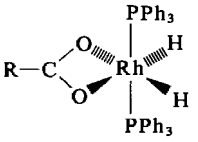
(27)



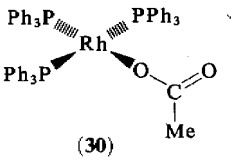
(28)

The intermediates formed in these reactions are unstable in presence of excess of the alkene, and catalysis rapidly ceases. The carbonate complex $[Rh(H)_2(PPr^i_3)_2(\eta^2\text{-}O_2COH)]$ (**28**) catalyzes

the hydrogenation of diphenylacetylene to *trans*-stilbene.[126] Here again, the *trans* isomer is believed to be formed directly. Complex (**28**) appears to be a more efficient catalyst for such reactions than (**26**), but details of the turnover numbers that can be achieved were not given.



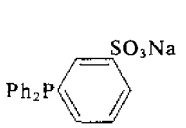
(**29**)



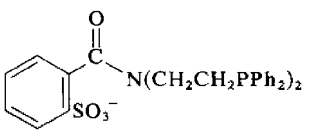
(**30**)

By addition of carboxylate anions to solutions of cationic rhodium-triphenylphosphine complexes under hydrogen, complexes of the type $[Rh(H)_2(O_2CR)(PPh_3)_2]$ have been isolated which have the structure (**29**). In benzene-methanol solution these complexes reduce the C=C double bond of activated alkenes.[127] Carboxylate complexes of the type $[Rh(O_2CR)(PPh_3)_3]$, which may be regarded as precursors of (**29**), have been prepared by addition of PPh_3 and a carboxylate anion to an acidic solution of $[Rh_2(OAc)_4]$.[128] They hydrogenate 1-hexene and 1-hexyne in benzene solution but at lower rates than $[RhCl(PPh_3)_3]$. Several carboxylate anions were used, the best results being obtained with the acetate. $[Rh(OAc)(PPh_3)_3]$ (**30**) in methanol solution gave rates superior to those obtained in benzene, and in presence of *p*-toluenesulfonic acid even better rates were obtained.[30] This was true for terminal, internal and cyclic alkenes and for both conjugated and non-conjugated dienes. By varying the acid/acetate ratio, a wide range of dienes could be hydrogenated to the monoene with high selectivity. The acid dependence was thought to be due to conversion of complex (**30**) to cationic species by protonation of the acetate group. Complex (**30**) is more easily prepared from $[RhCl_3 \cdot 3H_2O]$ directly[30] than by the original method.[128]

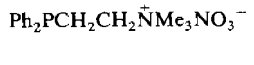
Another variation on the structure of $[RhCl(PPh_3)_3]$ is the complex $[Rh(PPh_3)_3(\eta^3\text{-}C_3H_5)]$, which has been shown to reduce 1-octene without isomerization occurring.[129] Water-soluble hydrogenation catalysts have been obtained using ligands such as (**31**)-(**33**) which contain strongly polar groups.



(**31**)



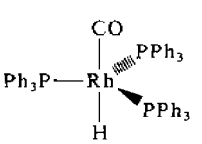
(**32**)



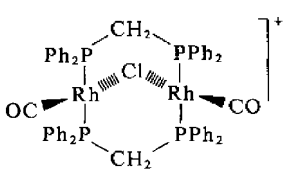
(**33**)

$[RhCl_3 \cdot 3H_2O]$ in presence of (**31**) was shown to hydrogenate cyclohexene in 1:1 mixtures of water and a polar organic solvent.[130] Similarly, rhodium complexes of (**32**) and ligands of related structure reduced activated alkenes.[131] $[RhCl(m\text{SPPh}_2)_3]$ ($m\text{SPPh}_2$ = **31**) hydrogenated 1-hexene, 2-hexene and cyclohexene in a two-phase system, the complex remaining in the aqueous phase.[132] $[Rh(nbd)(amphos)_2]^{3+}$ (amphos = **33**), also in a two-phase system, reduced 1-hexene and styrene.[133]

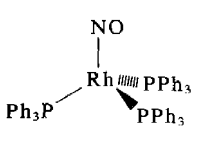
Although carbonyl groups generally tend to deactivate rhodium hydrogenation catalysts, a number of complexes have been studied. $[RhH(CO)(PPh_3)_3]$ (**34**), which is better known as a



(**34**)



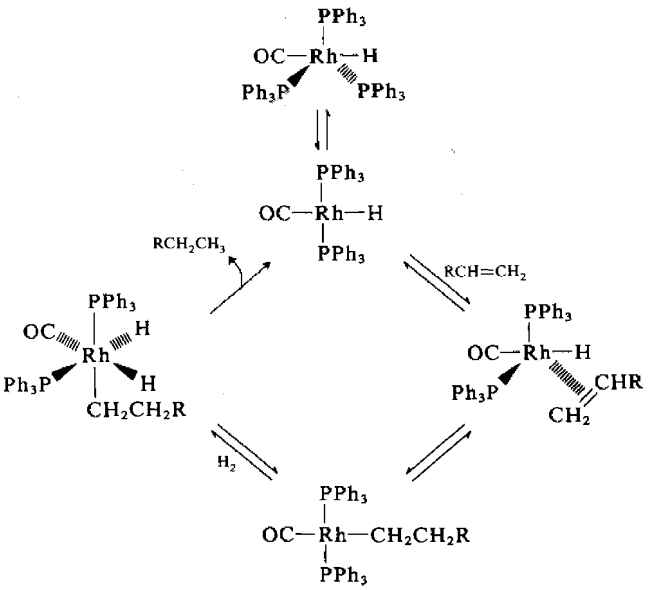
(**35**)



(**36**)

hydroformylation catalyst (see Section 61.2.4.4), also hydrogenates alkenes at normal temperature and hydrogen pressure.[134] The complex shows a marked preference for terminal double bonds. Alkynes, conjugated dienes and internal and cyclic alkenes were not hydrogenated under these conditions. Following a kinetic investigation of the hydrogenation of 1-hexene and 1-decene, the mechanism shown in Scheme 10 was proposed. The catalyst slowly loses its activity owing to dimerization according to equation (26).

$$2[RhH(CO)(PPh_3)_3] \rightarrow [Rh(CO)(PPh_3)_2]_2 + 2PPh_3 + H_2 \qquad (26)$$



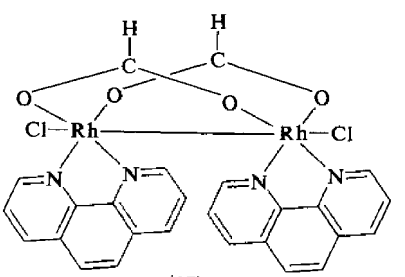
Scheme 10

In the hydrogenation of ethyl acrylate, it was shown that deactivation also occurred, but irradiation with a weak source of UV light led to reactivation and complete hydrogenation to ethyl propionate.[136]

Using the ligands $Ph_2PCH_2PPh_2$ (dpm) and $Ph_2AsCH_2PPh_2$ (dam) a series of complexes of the type $[Rh_2X(CO)_2L_2]^+$ (X = Cl, Br; L = dpm, dam) were introduced. These complexes have the so-called 'A-frame' structure illustrated in (**35**) for $[Rh_2Cl(CO)_2(dpm)_2]^+$. Terminal, internal and cyclic alkenes and terminal and internal alkynes were hydrogenated. Complex (**35**) appears to be the better catalyst, followed by its dam analogue. However, for the reduction of phenylacetylene to styrene, $[Rh_2(CN)_2(CO)_4(dpm)_2]$ was far more active than the other complexes.[137]

The nitrosyl complex $[Rh(NO)(PPh_3)_3]$ (**36**) catalyzes the hydrogenation of both 1-hexene and cyclohexene in dichloromethane as solvent and was also found to add deuterium to cyclohexene without H/D scrambling.[138] A further study extended the range of substrates hydrogenated to internal alkenes, to conjugated and non-conjugated dienes, activated alkenes and terminal and internal alkynes.[139]

Nitrogen ligands have played a minor role in homogeneous hydrogenation compared with those of phosphorus, but some such catalysts are known. The 1,10-phenanthroline complex (**37**) has been shown to hydrogenate cyclohexene.[140]



(37)

1,10-Phenanthroline and 2,2′-bipyridyl complexes have been studied in greater detail by Mestroni and co-workers.[141,142] A series of complexes of the type [Rh(chel)(HD)]X (chel = bipy, phen, 4,7-Me_2-phen, 5,6-Me_2-phen, 3,4,7,8-Me_4-phen; HD = 1,5-hexadiene; $X = PF_6^-$, BPh_4^-) were prepared. These complexes react with hydrogen to give solvated species, the hexadiene undergoing hydrogenation (equation 27; S = solvent).

$$[Rh(chel)(HD)]^+ + H_2 \xrightarrow{S} [Rh(chel)S_2]^+ + \text{hexane} \qquad (27)$$

In contrast to the phosphine analogues already mentioned, reaction (27) does not occur with the cod and nbd complexes. Further, reaction (28) occurs quantitatively on addition of cod to the hexadiene complexes.[141]

$$[Rh(chel)(HD)]^+ + cod \rightarrow [Rh(chel)(cod)]^+ + HD \quad (28)$$

In alkaline solution, the rhodium–hexadiene complexes hydrogenate ketones at normal temperature and hydrogen pressure. Carbon–carbon double bonds are also reduced. An excess of the nitrogen ligand was found to be advantageous in some cases and the ion $[Rh(bipy)_2]^+$, which is presumably solvated, reduced a range of ketones almost quantitatively. When equimolar mixtures of cycloalkenes and cyclic ketones were used as substrates in alkaline methanol, $[Rh(bipy)_2Cl_2]^+$ gave almost exclusive hydrogenation of the ketones. On the other hand, the C=C bond of unsaturated esters and ketones was preferentially reduced by $[Rh(bipy)S_2]^+$.[142] Clearly most interesting selectivities can be achieved with these catalysts.

The reaction of $[Rh_2Cl_2(C_8H_{14})_4]$ with 2-aminopyridine led to a species believed to be a cationic solvated rhodium(I)–aminopyridine complex. This was more active than $[RhCl(PPh_3)_3]$ or $[RuH(Cl)(PPh_3)_3]$ for the hydrogenation of cyclohexene. The mechanism was thought to involve oxidative addition of hydrogen to rhodium(I) prior to alkene coordination.[143]

James *et al.* have shown that dialkyl sulfide complexes of rhodium can act as homogeneous hydrogenation catalysts. The complex $[RhCl_3(SEt_2)_3]$ in DMA solution is believed to react with hydrogen according to equations (29)–(31).

$$[RhCl_3(SEt_2)_3] \rightarrow [RhCl_3(SEt_2)_2] + Et_2S \quad (29)$$

$$[RhCl_3(SEt_2)_2] + H_2 \rightarrow [Rh(H)Cl_3(SEt_2)_2]^- + H^+ \quad (30)$$

$$[RhCl_3(SEt_2)_2] + H_2 \rightarrow [Rh(H)Cl_2(SEt_2)_2] + H^+ + Cl^- \quad (31)$$

The rhodium(III) hydride then loses a proton to give a rhodium(I) complex which after coordination of the alkene oxidatively adds hydrogen. Ethylene, cinnamic acid and maleic acid were reduced.[144] $[RhCl_3(SBz_2)_3]$ was also an active catalyst for maleic acid hydrogenation.[145] By addition *in situ* of Et_2S to the cyclooctene complex $[RhCl(C_8H_{14})_2]_2$, species were obtained which exhibited the same kinetics as the rhodium(III) complexes in maleic acid hydrogenation.[146] The complex $[Rh_2(\mu\text{-}SBu^t)_2\{P(OMe)_3\}_4]$ and related complexes with mixed thiol bridges and with other phosphites have been shown to hydrogenate cyclohexene.[147]

The rhodium(II) complex $[Rh_2(OAc)_4]$ reduces terminal and cyclic alkenes, activated alkenes and alkynes.[148] Various polar solvents could be used, but DMF was preferred. Following a kinetic investigation of the hydrogenation of 1-decene, the mechanism shown in equations (32)–(35) was proposed.

$$[Rh_2(OAc)_4] + H_2 \rightleftharpoons [Rh_2H(OAc)_3] + H^+ + AcO^- \quad (32)$$

$$[Rh_2H(OAc)_3] + \text{alkene} \rightarrow [Rh_2H(\text{alkene})(OAc)_3] \quad (33)$$

$$[Rh_2H(\text{alkene})(OAc)_3] \rightleftharpoons [Rh_2(\text{alkyl})(OAc)_3] \quad (34)$$

$$[Rh_2(\text{alkyl})(OAc)_3] + H^+ + AcO^- \rightarrow [Rh_2(OAc)_4] + \text{alkane} \quad (35)$$

Unfortunately it is not known whether hydride and alkene coordinate to the same or different rhodium atoms in the dimer, but the former appears more probable in terms of our general mechanistic knowledge of hydrogenation. The observation of alkene isomerization during the reaction indicates that equation (34) is reversible.

Some other rhodium homogeneous hydrogenation catalysts and the substrates they reduce are collected in Table 3. Two reviews which concentrate on rhodium-catalyzed hydrogenation have appeared.[81,154]

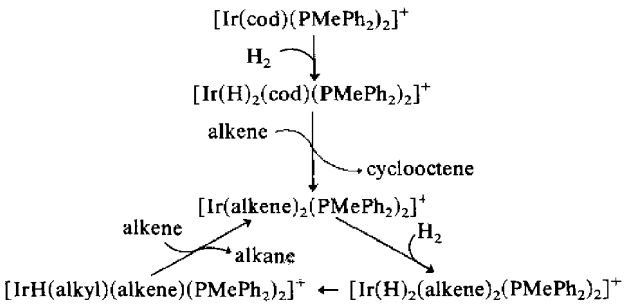
Table 3 Some Other Rhodium Hydrogenation Catalysts

Complex	*Substrate*	*Ref.*
$[RhH(C_2B_9H_{11})(PPh_3)_2]$	1-Hexene	149
$[Rh_2Cl_2(CO)_4]$	1,3-Pentadiene	150
$[Rh(cod)L_2]ClO_4$	1-Hexene, cyclohexene, dienes	151
L = MeCN, PhCN		
$[Rh(cod)L']ClO_4$	1-Hexyne	
L' = succinonitrile		
Rh amino acid complexes	Arenes	152
$[RhCl(HD)]_2$	Arenes, substituted	153
HD = 1,5-hexadiene	Arenes, aromatic heterocycles	

61.2.2.4 Iridium

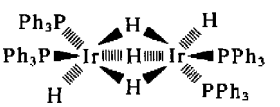
In acetic acid solution, $[Ir(H)_3(PPh_3)_3]$ (**38**) catalyzes the hydrogenation of 1-butanal to *n*-butanol at normal pressure of hydrogen and slightly above room temperature. Simple alkenes were not reduced under these conditions, but the C=C bonds of acrylic acid and methyl acrylate were. Acetate complexes were believed to be responsible for the catalysis.[155] In dichloromethane, (**38**) hydrogenated both ethylene and 1-hexene. Dissociation of one PPh_3 ligand to give the coordinatively unsaturated species $[Ir(H)_3(PPh_3)_2]$ was a necessary preliminary to catalysis.[156] Another bis(triphenylphosphine) species, $[Ir(H)_2(OCMe_2)_2(PPh_3)_2]^+$, has been shown to hydrogenate norbornadiene.[157] When (**38**) was used under a hydrogen pressure of 1 MPa, turnover numbers of more than 8000 could be achieved in aldehyde hydrogenation.[158]

Cationic complexes of the type $[Ir(cod)L_2]^+$ ($L = PPh_3$, $PMePh_2$), having a non-coordinating anion, efficiently hydrogenate alkenes and dienes.[159] These complexes oxidatively add hydrogen to give the corresponding dihydrides, $[Ir(H)_2(cod)L_2]^+$. The diene is then hydrogenated to cyclooctene. The proposed mechanism for $L = PMePh_2$ is shown in Scheme 11.

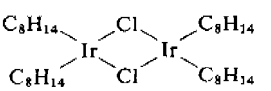


Scheme 11

Other phosphorus ligands used include PCy_3 and diphos. The complex $[Ir(cod)py(PPr^i)_3]^+$ was also active. After the cessation of hydrogenation, deactivation of the catalyst occurs rapidly.[160] This was caused by the formation of the dinuclear hydride $[Ir_2(H)_5L_4]^+$. The PPh_3 complex has the structure (**39**).



(**39**)

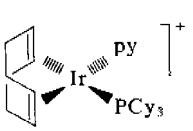


(**40**)

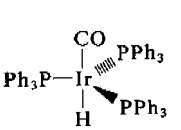
The pyridine complexes also undergo deactivation, but the nature of the resulting complex is unknown. A series of *para*-substituted triarylphosphines was used to give the complexes $[Ir(cod)\{P(p\text{-}XC_6H_4)_3\}_2]^+$ (X = MeO, Me, H, F, Cl).[161] The rate of hydrogenation of 1-heptene and 1,4-cyclohexadiene increased with the electron releasing ability of the substituent. It was thought that the more basic phosphines favoured both the oxidative addition of hydrogen and alkene coordination. Deactivation of the catalyst again occurred after complete hydrogenation of the alkene.

$[IrCl(PPh_3)_3]$, the iridium analogue of Wilkinson's catalyst (**23**), does not function as a hydrogenation catalyst under mild conditions, as the necessary dissociation of one PPh_3 ligand does not occur. However, bis(triphenylphosphine) species prepared directly from $[IrCl(C_8H_{14})_2]$ (**40**) and the ligand were found to be about 10 times as active as (**23**). There was a marked preference for terminal over internal alkenes and the isomerization activity was much greater than with (**23**).[162] In a further study using complexes of the type $[IrCl(cod)(PPh_{3-x}Cy_x)]$, it was found that for all four phosphines the highest activity for 1-hexene hydrogenation was exhibited at P/Ir = 1. The PCy_3 and $PPhCy_2$ complexes were most effective.[164]

The complex $[Ir(cod)py(PCy_3)]^+$ (**41**) as the PF_6^- salt has been found to be superior to complex (**23**) in the selective hydrogenation of steroids to the 5α product.[165] Indenones and a series of substituted cyclohexenols could also be hydrogenated in good yield and with generally very high selectivity with (**41**).[166] A brief summary of some of the above chemistry is available.[167]



(**41**)



(**42**)

$[IrH(CO)(PPh_3)_3]$ (**42**) catalyzes the hydrogenation of ethylene, butadiene and dimethyl maleate. The rate of its reaction with hydrogen is far greater than that of hydrogenation. Oxidative addition and dissociation of PPh_3 give the species $[Ir(H)_3(CO)(PPh_3)_2]$, which then enters the catalytic cycle.[168,169] A precise mechanism could not be defined and it appears that this is in any case dependent on the alkene.[170] For the hydrogenation of 1,3-butadiene, equations (36)–(44) were postulated. η^3-C_4H_7 represents the trihapto-1-methylallyl group.

$$[IrH(CO)(PPh_3)_3] + H_2 \rightarrow [Ir(H)_3(CO)(PPh_3)_2] + PPh_3 \quad (36)$$

$$[Ir(H)_3(CO)(PPh_3)_2] + C_4H_6 \rightleftharpoons [Ir(CO)(PPh_3)_2(\eta^3\text{-}C_4H_7)] + H_2 \quad (37)$$

$$[IrH(CO)(PPh_3)_3] + C_4H_6 \rightleftharpoons [Ir(CO)(PPh_3)_2(\eta^3\text{-}C_4H_7)] + PPh_3 \quad (38)$$

$$[Ir(CO)(PPh_3)_2(\eta^3\text{-}C_4H_7)] + H_2 \rightleftharpoons [Ir(H)_2(CO)(PPh_3)_2(\sigma\text{-}C_4H_7)] \quad (39)$$

$$[Ir(H)_2(CO)(PPh_3)_2(\sigma\text{-}C_4H_7)] + PPh_3 \rightarrow [IrH(CO)(PPh_3)_3] + C_4H_8 \quad (40)$$

$$[Ir(H)_2(CO)(PPh_3)_2(\sigma\text{-}C_4H_7)] + PPh_3 \rightarrow [IrH(CO)(PPh_3)_3] + C_4H_6 + H_2 \quad (41)$$

$$[Ir(H)_2(CO)(PPh_3)_2(\sigma\text{-}C_4H_7)] \rightarrow [IrH(CO)(PPh_3)_2] + C_4H_8 \quad (42)$$

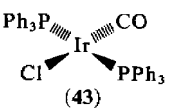
$$[IrH(CO)(PPh_3)_3] \rightleftharpoons [IrH(CO)(PPh_3)_2] + PPh_3 \quad (43)$$

$$[IrH(CO)(PPh_3)_2] + H_2 \rightleftharpoons [Ir(H)_3(CO)(PPh_3)_2] \quad (44)$$

In the reduction of dimethyl maleate, isomerization to fumarate was much faster than hydrogenation.[171] In addition to a mechanism broadly similar to that for butadiene, a further pathway was thought to operate which involved an *ortho*-metallation of one PPh_3 ligand, as shown in equations (45) and (46).

$$[Ir(alkyl)(CO)(PPh_3)_2] \rightarrow [\overline{Ir(C_6H_4PPh_2)}(CO)PPh_3] + alkane \quad (45)$$

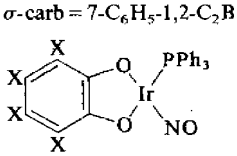
$$[\overline{Ir(C_6H_4PPh_2)}(CO)(PPh_3)] + H_2 \rightarrow [IrH(CO)(PPh_3)_2] \quad (46)$$



(**43**)

The iridium(I) complex $[IrCl(CO)(PPh_3)_2]$ (**43**), generally known as Vaska's compound, has played a most important role in the study of oxidative addition and Strohmeier and co-workers have shown that under appropriate conditions it is an extremely efficient hydrogenation catalyst. With activated alkenes, turnover numbers of several thousands could be achieved at raised temperature and pressure. $[IrCl(CO)(PCy_3)_2]$ gave even better results, and with ethyl crotonate

Table 4 Some Other Homogeneous Iridium-catalyzed Hydrogenations

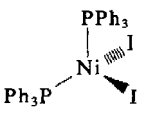
Complex	*Substrate*	*Ref.*
$[IrCl(cod)L]$ $L = PPh_3$, PCy_3 $[Ir(OAc)(cod)]_2$ $[Ir(OAc)(cod)PPh_3]$	1-Hexene	178
$[IrH(Cl)(BF_4)N_2(PPh_3)_2]$	Cyclohexene	179
$[Ir_2Cl_2L]$ $L = C_6H_4\{CH_2P(CH_2CH_2PPh_2)_2\}_2$	Hexene, cyclohexene	180
$[Ir(\sigma\text{-carb})CO(PhCN)PPh_3]$ σ-carb = 7-C_6H_5-1,2-$C_2B_{10}H_{10}$	Alkenes, alkynes	181
 X = H, Br	Alkenes, dienes, trienes	182
$[IrX(CO)L_2]$ X = Cl, Br, I $L = PCy_3$, PPh_3, $P(OPh)_3$	Alkenes, activated alkenes	183, 184
$[Ir(cod)(PhCN)L]^+$ $L = PCy_3$, PPh_2(neomenthyl)	Activated alkenes	185
$[IrCl(CO)(PCy_3)_2]$ $[IrCl(PPh_3)_3]$ $[IrH(CO)(PPh_3)_3]$ $[Ir(H)_3(PPh_3)_3]$	Alkenes, activated alkenes, ketones	186

turnover numbers over 150 000 were attained.[172] The precise mechanism of homogeneous hydrogenation with (**43**) is still uncertain.[173] In diene hydrogenation, which occurs with high selectivity towards monoene formation, η^3-allyl complexes are believed to be formed.[174] 1,4-Cyclohexadiene,[175] but-2-yne-1,4-diol[176] and dimethyl maleate[177] have also been hydrogenated using complex (**43**) as catalyst. Some other reports of homogeneous iridium hydrogenation catalysts are given in Table 4.

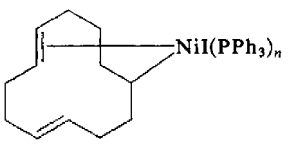
61.2.2.5 Nickel, Palladium and Platinum

$[NiI_2(PPh_3)_2]$ (**44**) hydrogenates linear and cyclic dienes, both conjugated and non-conjugated. With the former, 1,4-addition of hydrogen predominates, the reaction involving η^3-allyl intermediates. The complex also reduces 1,5,9-cyclododecatriene.[187] In a further study of this reaction, (**44**) was believed to activate hydrogen by heterolytic cleavage (equation 47). The reaction is then believed to proceed by alkylene complexes such as (**45**) to give the monoene.[188] These reactions require hydrogen pressures well above normal.

$$[NiI_2(PPh_3)_2] + H_2 \xrightarrow{PPh_3} [Ni(H)I(PPh_3)_2] + Ph_3P{\cdot}HI \qquad (47)$$



(**44**)



(**45**)

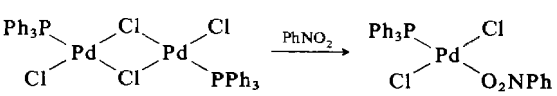
Treatment of $[Ni(acac)_2]$ with $Al_2Et_3Cl_3$ in presence of PPh_3 gave solutions which selectively hydrogenated cyclic dienes to monoenes[189] at normal hydrogen pressure. $[Ni(acac)_2]$ alone was shown to hydrogenate cyclohexene, but again only at raised hydrogen pressure. From a kinetic study of the reaction, alkene coordination was concluded to precede hydrogen activation.[190]

Palladium complexes of the general kind $[PdX_2L_2]$ (X = halogen, L = phosphine), either alone or in presence of $SnCl_2$, hydrogenate linear and cyclic dienes including sterically hindered ones at raised hydrogen pressure.[187,191] An allyl complex, $[PdCl(PPh_3)(\eta^3\text{-}C_8H_{13})]$, was isolated from these solutions and was shown to be a more active catalyst than $[PdCl_2(PPh_3)_2]$. An excess of PPh_3 poisoned the reaction but neither catalyst was affected by an excess of chloride ion.

The complex $[PdCl(PPh_3)(\eta^3\text{-}C_4H_7)]$ and related complexes have independently been shown to hydrogenate linear and cyclic octadienes.[192] The allyl group is first reduced, creating coordinative unsaturation. Complexes of diphosphines such as $[PdCl_2(diphos)]$ and $[Pd(diphos)_2]$ hydrogenate acetylene, monoenes, dienes and trienes.[193] These reactions were accelerated by exposure of the catalyst solution to oxygen, possibly due to the generation of coordinative unsaturation by partial oxidation of the phosphorus ligand to the phosphine oxide.

In DMF as solvent, $PdCl_2$ or $[PdCl_2(DMF)_2]$ will catalyze the hydrogenation of conjugated dienes and alkynes to alkenes.[194] The above systems quite generally give selective reduction of dienes to monoenes.

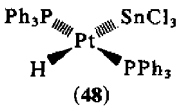
In presence of pyridine, solutions of $[Pd(acac)_2]$ catalyzed the reduction of nitrobenzene to aniline at normal pressure of hydrogen and the complex $[PdH(acac)(PhNO_2)py]$ was isolated. The dinuclear complex $[Pd_2Cl_4(PPh_3)_2]$ (**46**) also catalyzes the reduction of nitrobenzene. At normal hydrogen pressure, complete reduction to aniline occurred.[196] A nitrobenzene complex, believed to be an intermediate in the reaction, was isolated (equation 48).



(**46**) (48)

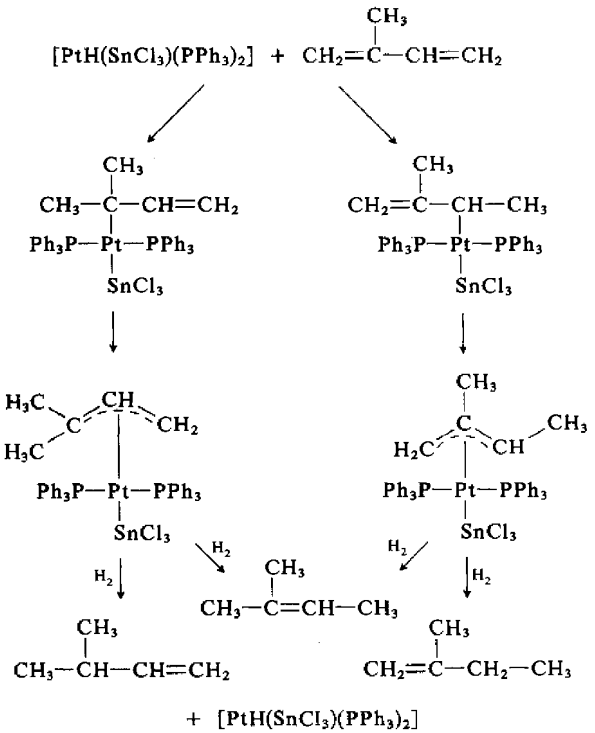
Platinum complexes of the general type $[PtX_2L_2]$ (X = halogen, pseudohalogen; L = phosphine, arsine, sulfide, selenide) in presence of $SnCl_2$ hydrogenate terminal alkenes,[197-199] linear and cyclic dienes and trienes,[187,198,199] unsaturated nitriles[198] and long-chain alkenes such as methyl linoleate[200] and soybean oil.[201] In general, dienes are reduced to monoenes selectively. These reactions require raised hydrogen pressure (3.4–5 MPa).

The complex $[PtCl_2(PPh_3)_2]$ has been most generally used.[198,199,201] With $SnCl_2$, this gives $[PtCl(SnCl_3)(PPh_3)_2]$ (**47**). Complex (**47**) then gives the hydride $[PtH(SnCl_3)(PPh_3)_2]$ (**48**) with



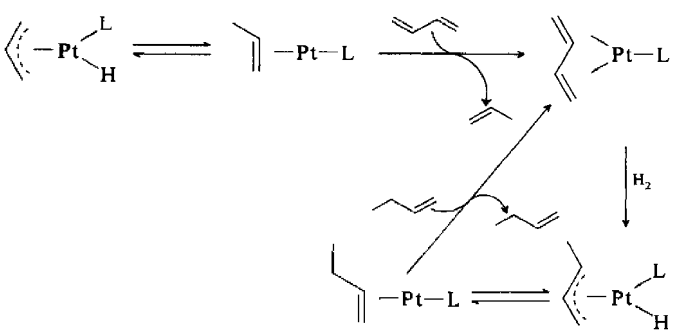
(48)

hydrogen.[187,199,200] Other Lewis acids than $SnCl_2$ have been tried but were far less effective.[200] For the hydrogenation of isoprene the mechanism shown in Scheme 12 has been proposed.[187] This mechanism requires the heterolytic cleavage of the hydrogen molecule but does not show the formation of a hydridoalkene–hydride complex, which is generally believed to be an intermediate stage in hydrogenation.[21]



Scheme 12

$[PtCl(SnCl_3)(PPh_3)_2]$ and related complexes have been shown to be useful for the partial hydrogenation of soybean oil.[201] Complexes of the type $[PtCl_2LL']$ (L = PPh_3; L' = sulfide, amine) are better catalysts for the hydrogenation of styrene than the corresponding $[PtCl_2L_2]$ or $[PtCl_2L'_2]$ complexes. Here again, $SnCl_2$ was present.[202] The ligands L' were shown to be more labile than PPh_3 and their value appears to lie in facilitating the production of coordinative unsaturation. This, in turn, may lead to the alkene complex lacking in Scheme 12. Further evidence for monophosphine species is provided by the complexes $[PtHL(\eta^3\text{-}C_3H_5)]$ (L = PCy_3, PBu^t_3), which catalyze the hydrogenation of dienes to monoenes even at −78 °C.[203] The mechanism shown in Scheme 13 was proposed. Addition of diene to the η^3-allyl complex was shown to cause immediate displacement of propylene. No reaction with hydrogen occurred in absence of diene.



Scheme 13

$[PtH(NO_3)(PEt_3)_2]$ at raised temperature and pressure hydrogenates monoenes and dienes to alkanes. The reduction of dienes was found to be more difficult than that of monoenes, in contrast to the behaviour of other platinum catalysts.[204]

Methanolic solutions of $H_2PtCl_6 \cdot 2H_2O$ and $SnCl_2 \cdot 2H_2O$ catalyze the hydrogenation of ethylene and acetylene under mild conditions.[205] Hydrogen activation was attributed to equation (49). This step was believed to precede coordination of ethylene, after which alkene insertion and protonation of the platinum–ethyl bond complete the cycle. In isopropanol in the presence of HBr this system has been shown to hydrogenate a range of simple and activated alkenes at normal temperature and hydrogen pressure.[206] The hydrogenation of methyl cinnamate by $[PtCl_2(SnCl_3)_2]^{2-}$ was shown by deuteration studies to involve a *cis* or suprafacial transfer of the first hydrogen atom to the double bond. The second hydrogen transfer was non-specific.[207]

$$[Pt(SnCl_3)_5]^{3-} + H_2 \rightarrow [PtH(SnCl_3)_4]^{3-} + H^+ + SnCl_3^- \quad (49)$$

61.2.2.6 Other Metals

$[Os(H)_4(PEtPh_3)_3]$ catalyzes the hydrogenation of 1-octene at normal pressure and raised temperature, but considerable isomerization occurs. The complex can be recovered unchanged after the reaction. The *cis* complex $[Os(H)_2(PEtPh_2)_4]$ catalyzes isomerization more rapidly than hydrogenation.[208]

$[CuBr(PPh_3)_3]$ hydrogenates nitrobenzene, giving nitrosobenzene, azobenzene and aniline at high temperature. The dinuclear complexes $[Cu_2(H)_2Br_2(PPh_3)_2]$ and $[Cu_2Br_2(PPh_3)_4(PhN{=}NPh)]$ were isolated from the reaction and are believed to be intermediates.[209]

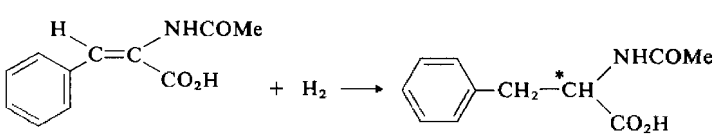
There are a number of reviews available on homogeneous hydrogenation. Specialized reviews are available on hydrogenation with phosphine complexes of rhodium,[154] on hydrogenation of arenes,[210] on hydrogenation with water-soluble catalysts,[211] and on mechanistic aspects.[81] There are general reviews covering the older[212–216] and more recent[21,217,218] literature.

61.2.3 ASYMMETRIC HYDROGENATION

61.2.3.1 C=C Bonds

The introduction of the highly efficient homogeneous hydrogenation catalyst $[RhCl(PPh_3)_3]$ (**23**)[79] led to attempts to adapt this system to catalytic asymmetric homogeneous hydrogenation by the introduction of chiral phosphorus ligands in place of PPh_3. In 1968 the groups of Knowles[219] and Horner[220] both demonstrated the use of methyl-*n*-propylphenylphosphine and a rhodium compound in asymmetric hydrogenation.

Knowles *et al.* used a sample of (−)-MePr^{n}PhP which was of only 60% optical purity together with $RhCl_3 \cdot 3H_2O$ to hydrogenate α-phenylacrylic acid to hydratropic acid, which had an optical purity of 15%. Horner *et al.* used (+)-MePr^{n}PhP with $[RhCl(1,5\text{-hexadiene})]_2$ to hydrogenate α-ethylstyrene to 2-phenylbutane having an optical purity of 8%. The method of preparing the catalyst *in situ* from a rhodium(I) complex of this type and the phosphorus ligand has now found general application in asymmetric catalysis. For this very moderate start, asymmetric catalytic hydrogenation has now made dramatic progress. Optical yields of over 90% are now commonplace, and 97–99% is not unusual. From the start, there was great interest in the production of amino acids by asymmetric hydrogenation and α-acetamidocinnamic acid, its derivatives and related compounds rapidly became the principal alkenes studied (equation 50).



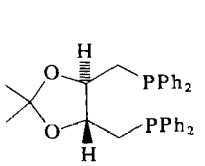
(50)

Initial efforts concentrated on monodentate ligands in which the phosphorus atom itself was the asymmetric centre. Morrison and co-workers introduced the ligand neomenthyldiphenylphosphine, in which the phosphorus atom itself is not chiral.[221] Such a phosphine is easily prepared from a natural, chiral substance and does not require the resolution step necessary for those chiral

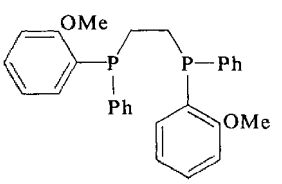
at phosphorus. Using this ligand and a rhodium(I)-ethylene or -diene complex, (*E*)-β-methylcinnamic acid could be hydrogenated with an enantiomer excess of 61%, far surpassing the previous results. A further important step was taken by Kagan, who introduced the first chelating diphosphine ligand to asymmetric hydrogenation.[222,223] His ligand, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, generally abbreviated to DIOP (**49**; Figure 1), could be used with $[RhCl(C_8H_{14})_2]_2$ to hydrogenate α-acetamidocinnamic acid in an optical yield of 72%. Other amino acid precursors could be reduced in up to 80% optical yield. DIOP has the same advantage as neomenthyldiphenylphosphine of being prepared from a chiral natural substance, in this case L-tartaric acid. The value of the α-acetamido group in these reactions was soon recognized.[223] The complexity of the full chemical names of most ligands used in asymmetric homogeneous catalysis has led to the general introduction of abbreviated names such as DIOP and this practice will be followed here.

Knowles next reported optical yields of up to 90% in the hydrogenation of further α-acetamidocinnamic acid derivatives, still using monodentate phosphines chiral at phosphorus. Again the catalysts were prepared *in situ* from the ligand and $[RhCl(1,5\text{-hexadiene})_2]$ or a related complex. The best optical yield of 90% was obtained using cyclohexyl(*o*-anisyl)methylphosphine (CAMP).[224]

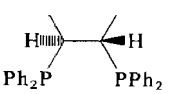
The above reports laid the basis for catalytic asymmetric hydrogenations giving optical yields of close to 100%. Quite generally rhodium was the metal used with a chelating diphosphine as ligand. It seems to matter but little from the point of view of the enantiomer excess whether the asymmetric centre(s) in the ligand are at phosphorus or elsewhere. α-Acylamino-cinnamic and -acrylic acid derivatives have generally been the substrates used. The value of an alkene which can act as a bidentate chelate has long been recognized. Reviews of the early literature are available.[225–228] Those rhodium–diphosphine systems which have led to optical yields of 90% or better are summarized below. The reviews given at the end of this section should be consulted for other more recent reports.



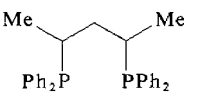
(**49**) DIOP



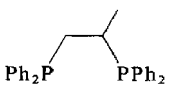
(**50**) DIPAMP



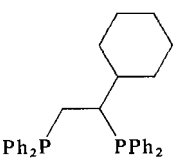
(**51**) CHIRAPHOS



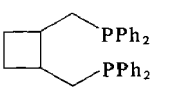
(**52**) SKEWPHOS



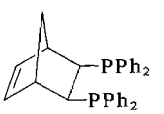
(**53**) PROPHOS



(**54**) CYCPHOS



(**55**)



(**56**) NORPHOS

Figure 1 Some diphosphine ligands used in asymmetric hydrogenation

$[RhCl(C_8H_{14})_2]$ in presence of DIOP (**49**) gave an optical yield of 92% in the hydrogenation of α-acetamidocrotonic acid.[229] The complex [Rh(cod)(*R*,*R*-DIPAMP)]$^+$ reduced a number of α-acylamino-cinnamic and -acrylic acid derivatives in optical yields of 93–96%.[230] DIPAMP is the ligand used in the Monsanto synthesis of L-dihydroxyphenylalanine (L-DOPA) by rhodium-catalyzed asymmetric hydrogenation. L-DOPA is important in the treatment of Parkinson's disease. The complexes [Rh(diene)(*S*,*S*-CHIRAPHOS)]$^+$ (diene = cod, nbd) were used to prepare *R*-phenylalanine, *R*-leucine and *R*-tyrosine in optical yields of 99, 100 and 92% respectively as the *N*-benzyl derivatives by hydrogenation of the appropriate dehydro compounds.[231] The *N*-acetyl derivatives of *R*-alanine, *R*-phenylalanine, *R*-tyrosine and *R*-DOPA were obtained in 90–98% optical yields by the hydrogenation of the corresponding dehydroamino acid derivatives using [Rh(nbd)(*S*,*S*-SKEWPHOS)]$^+$ as catalyst. When the related ligand (*S*)-1,3-bis(diphenylphosphino)butane, which possesses only one asymmetric centre, was used in place of *S*,*S*-SKEWPHOS, the optical yields dropped to 1–20%. This was attributed to the phenyl groups being in an achiral array in this case.[232] Both of these ligands form six-membered chelate rings. When (*R*)-1,2-bis(diphenylphosphino)propane, or *R*-PROPHOS (**53**), was used in similar hydrogenations, the optical yields were again 91–93%, indicating that in the less mobile five-membered chelate ring

one asymmetric centre is sufficient.[233] The use of (*R*)-1-cyclohexyl-1,2-bis(diphenylphosphino)ethane, (*R*)-CYCPHOS (**54**), in which the methyl group of PROPHOS is replaced by the more bulky cyclohexyl ring, led to optical yields of 90–98% in such hydrogenations.[234]

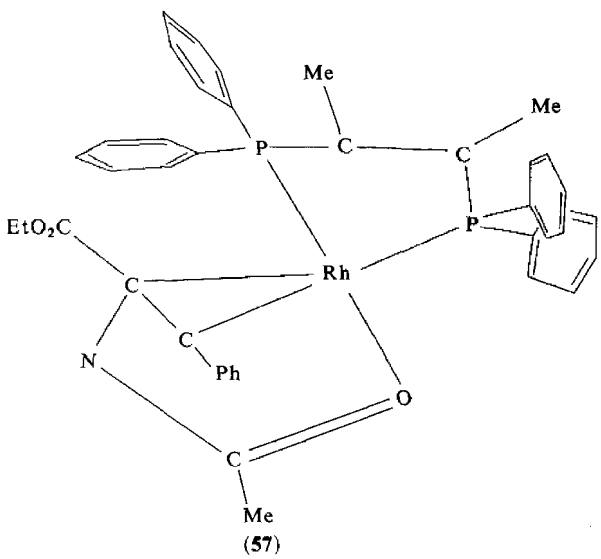
The cyclobutane derivative (**55**) gave an optical yield of 91% in the hydrogenation of α-acetamidocinnamic acid. The catalyst was here prepared *in situ* from $[RhCl(1,5\text{-hexadiene})]_2$. The corresponding 1,2-derivative of cyclopentane gave an optical yield of only 73% and the cyclopropane and cyclohexane derivatives gave 15% and 36% respectively.[235] $[RhCl(cod)_2]$ in presence of the norbornadiene-based ligand NORPHOS (**56**) gave up to 96% optical yields with α-acetamidocinnamic acid as substrate.[236]

The above reports indicate that those diphosphines which may be regarded as derivatives of 1,2-bis(diphenylphosphino)ethane and which form five-membered chelate rings are easily adapted to use in asymmetric synthesis, the introduction of a single asymmetric centre in the carbon backbone being sufficient to give high optical yields (PROPHOS, CYCPHOS, NORPHOS). Two such centres (CHIRAPHOS), or asymmetry at both phosphorus atoms (DIPAMP), also leads to very high optical yields. For those diphosphines which form six- or seven-membered rings, the necessary asymmetric induction is less readily achieved. A number of comparative studies of phosphorus ligands in asymmetric hydrogenation catalysed by rhodium complexes have appeared.[237–240] Considerable ingenuity has been shown in designing ligands for asymmetric hydrogenation and some other rhodium catalysts which lead to very high optical yields are collected in Table 5. Chiral ligands will be found there and in Figure 1.

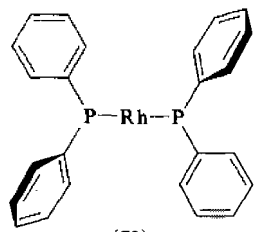
A number of groups have shown interest in the mechanism of asymmetric hydrogenation, principally of (α)-*Z*-acetamidocinnamic acid and its derivatives. Kagan and co-workers have shown that *cis* addition of deuterium occurs to the *Z* isomer. Rhodium complexes of DIOP were used here.[255] Koenig and Knowles obtained similar results with the ligands DIPAMP, cyclohexyl(*o*-anisyl)methylphosphine and others.[256] Both groups showed that *E*–*Z* isomerization occurred during the hydrogenations.

NMR spectroscopy has been used to study the species formed in solution by interaction of cinnamic acid derivatives with asymmetric hydrogenation catalysts.[257,258] Such studies are necessarily limited to those species which accumulate in adequate concentration and have sufficiently long lifetimes for observation by NMR. In catalytic reactions as rapid as those described here, such complexes appear likely to be outside rather than in the operating catalytic cycle.[91]

Halpern and co-workers have carried out a detailed investigation of the mechanism of the asymmetric hydrogenation of methyl (MAC) and ethyl (EAC) (*Z*)-α-acetamidocinnamate by rhodium complexes of the ligands DIPAMP (**50**) and CHIRAPHOS (**51**).[259] Coordination of alkene precedes the oxidative addition of hydrogen. For both ligands, one of the two possible diastereoisomers of the rhodium–diphosphine–alkene complex predominates in solution to a large extent. From the reaction of EAC with the *S,S*-CHIRAPHOS complex, this diastereoisomer has been isolated. Its structure is represented in (**57**).[260]



(**57**)



(**58**)

A feature of this structure is the arrangement of the four phenyl groups of the CHIRAPHOS ligand. Each PPh_2 unit has one phenyl group presenting an edge and one a face towards the

Table 5 Some Other Highly Selective Asymmetric Hydrogenation Catalysts

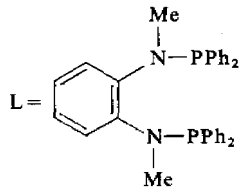
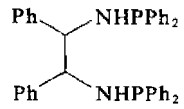
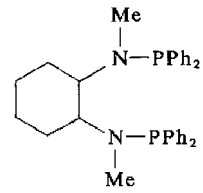
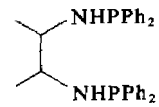
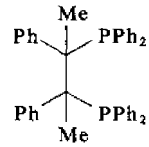
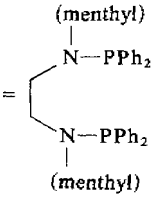
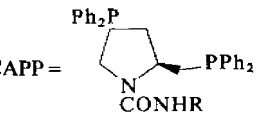
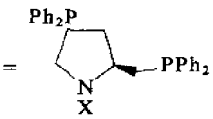
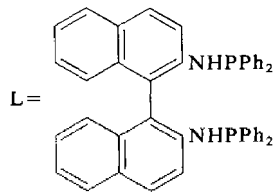
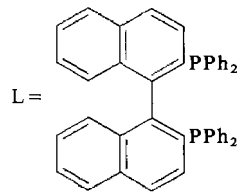
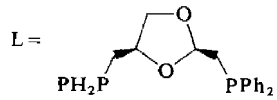
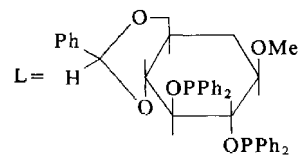
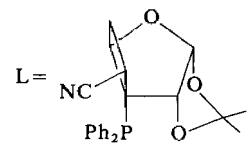
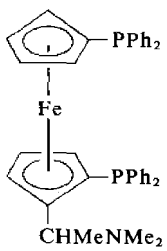
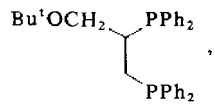
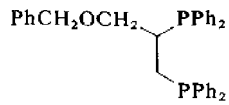
Catalyst	*Substrate*	% *e.e.*[a]	*Ref.*
$[Rh(cod)L]^+$	α-Acylaminoacrylic acids		241, 242
L = 		91-94	
L = 		93	
$[Rh(cod)L]^+$	α-Acylaminocinnamic acids		243
L = 		92	
L = 		93-94	
$[Rh(cod)L]^+$	α-Acetamidocinnamic acid	94	244
L = 			
$[Rh(cod)L]^+$	α-Acetamidocinnamic acid	91-93	245
L = 			
$[Rh(diene)CAPP]^+$ diene = cod, nbd	α-Acetamidocinnamic acid	91-98	246
CAPP =  R = aryl, alkyl			
$[RhCl(1,5\text{-hexadiene})]_2$ + L	α-Acetamidocinnamic acid	91	247
L =  X = H (PPM) X = CO_2Bu^n (BPPM)			

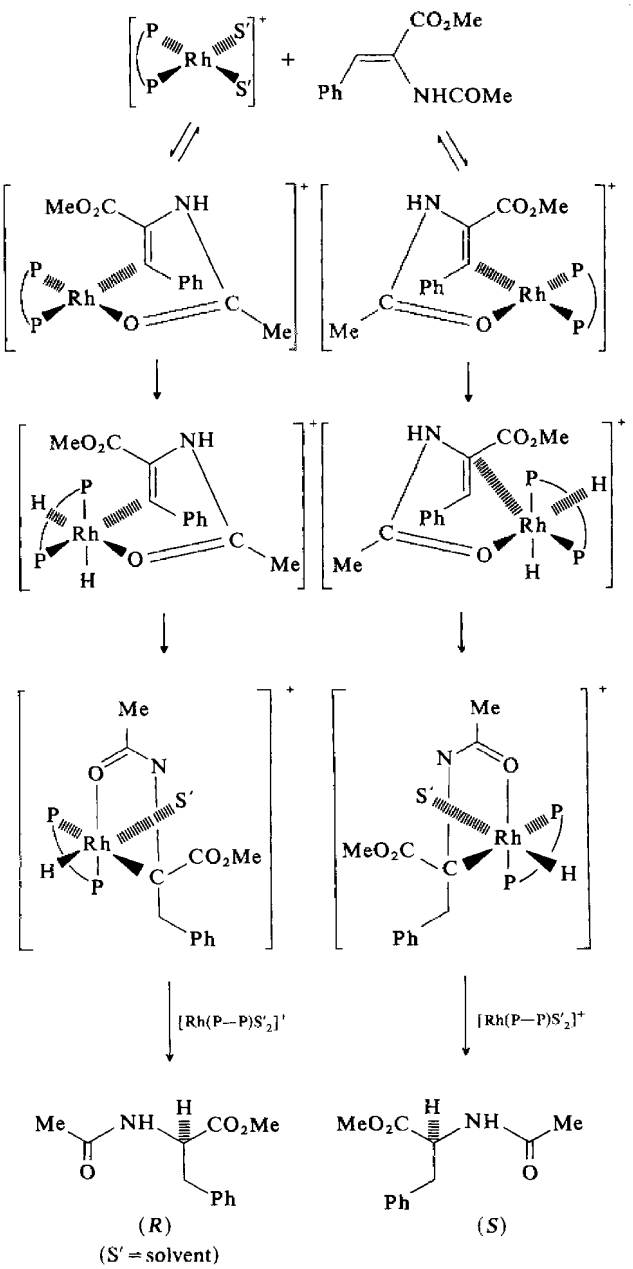
Table 5 (*continued*)

Catalyst	*Substrate*	% *e.e.*	*Ref.*
$[RhCl(C_8H_{14})_2]_2 + L$ L = 	α-Benzoylaminocinnamic acid	95	248
$[RhL(MeOH)_2]^+$ L = 	α-Benzoylaminocinnamic acid	98	249
$[Rh(cod)L]^+$ L =  (DIOXOP)	α-Acetamidocinnamic acid	90	250
$[Rh(nbd)L]^+$ L = 	α-Acetamido-acrylic and -cinnamic acids	90–91	251
$[RhCl(C_8H_{14})_2]_2 + L$ L = 	α-Acetamidocinnamic acid	92	252
$[RhCl(1,5\text{-hexadiene})]_2 +$ 	α-Acetamidocinnamic acid	93	253
$[Rh(nbd)L]^+$ L =  , 	N-Acetamidoacrylic acid, *N*-benzoylaminocinnamic acid, 4-acetoxy-3-methoxy-α-acetamidocinnamic acid	91–92	254

[a] e.e. = enantiomer excess.

alkene. This is shown more clearly in (**58**). This arrangement, which appears to be common to many rhodium–diphosphine complexes used in asymmetric hydrogenation, accounts for the chiral recognition by the rhodium atom of the alkene and explains the preponderance of one diastereoisomer of the [Rh(EAC)(*S,S*-CHIRAPHOS)]$^+$ complex.

Halpern has shown that this predominant isomer exhibits negligible activity towards the oxidative addition of hydrogen. The minor isomer, which could be detected in solution for DIPAMP but not for CHIRAPHOS, reacts far more rapidly with hydrogen and is responsible for producing the major enantiomer of the hydrogenation product. The optical selectivity is thus due to this difference in reaction rates and not simply to the preferred manner of coordination of the alkene to the rhodium–diphosphine species.[259,260] The precise reasons for this large difference in the rates of reaction of the two diastereoisomers with hydrogen are not yet known. The full mechanism is shown in Scheme 14.



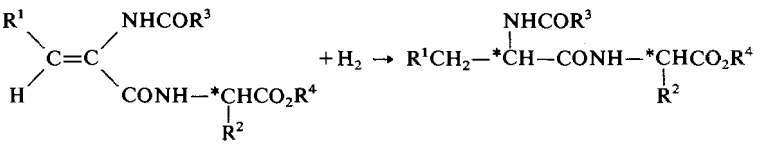
Scheme 14

The mechanism requires that the initial alkene coordination step be reversible, otherwise all of the rhodium would soon be present as the major diastereoisomer of the alkene complex and the reaction could then only proceed by this route, reversing the optical selectivity and drastically

reducing the rate. If the hydrogen pressure were to be increased, the degree of reversibility of this step would be *reduced* through increased competition by the oxidative addition of hydrogen. The selectivity would then become increasingly dependent on the mode of coordination of the alkene, leading to a reduction in the optical yield, with a possible reversal of the optical selectivity at sufficiently high pressure. Such an inverse dependence of optical yield on hydrogen pressure has been observed in asymmetric hydrogenations.[259,260]

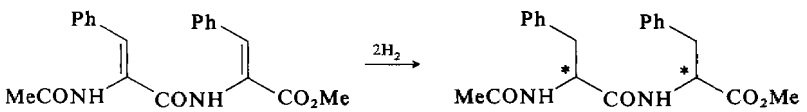
It is noteworthy that, at normal temperature and hydrogen pressure, these systems not only give optical selectivities very close to 100%, but also show activities well up in the range previously thought to be attainable only by enzymes. That this is possible with such comparatively simple transition metal complexes indicates how prodigal Nature has been in constructing its own catalysts.

Following the success in producing amino acids by asymmetric hydrogenation, this research has been extended to dipeptides. Using rhodium complexes of the same or similar ligands to those above, the hydrogenation of dehydrodipeptides is also possible in optical yields in the range of 90-98% (equation 51).[261-264]



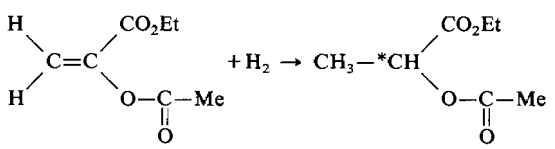
(51)

Poulin and Kagan have shown that a double asymmetric hydrogenation can be carried out on the same dipeptide precursor with excellent optical selectivity (equation 52). [Rh(cod)(*R,R*-DIPAMP)]$^+$ was used as catalyst. The major diastereoisomer of the product, which had the *S,S*-configuration, showed an optical purity of better than 95%.[265]



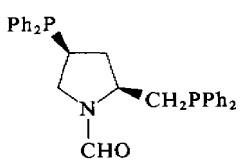
(52)

Efficient asymmetric hydrogenation of alkenes other than the amino acid and dipeptide precursors described above has met with only limited success. This appears to be at least in part due to the inability of many alkenes to function as bidentate chelates. Ethyl 2-acetoxyacrylate was hydrogenated with an enantiomer excess of 89% using [Rh(cod)(*R,R*-DIPAMP)]$^+$, giving the *S*-enantiomer (equation 53). The ligands CHIRAPHOS, PROPHOS, DIOP, BPPM and CAMP were less effective.[266]



(53)

Itaconic acid and its derivatives represent the only other alkene type which has so far been reduced with optical yields of over 90%. Using the usual cationic rhodium–diene (cod) precursor, a best optical yield of 94% was obtained with the diphosphine FPPM (**59**). The presence of triethylamine was necessary.[267] With the related BPPM (Table 5), again in presence of triethylamine, optical yields up to 92% were achieved.[268] [Rh(cod)(DIPAMP)]$^+$ gave an optical yield of 88% for the dimethyl ester of itaconic acid, and 90% with a monoamide of α-methyleneglutaric acid.[269]

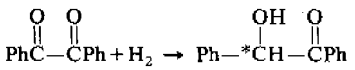


(**59**) FPPM

Several recent reviews on catalytic asymmetric hydrogenation are available. The mechanistic studies have been summarized by Halpern.[81,259] The synthesis and use of phosphorus(III) ligands have been reviewed by Horner.[270] Ferrocene-based and nitrogen-containing phosphorus ligands have also been covered.[271] General reviews of the subject have appeared.[272-275]

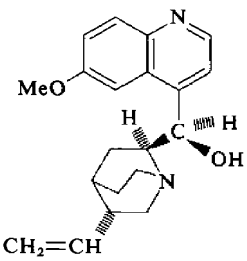
61.2.3.2 C=O Bonds

The asymmetric hydrogenation of C=O bonds have now been achieved in optical yields up to 95%, rivalling the performance of alkenes. Here also, rhodium complexes have been used almost exclusively, but some success has been obtained with cobalt catalysts. Using $[Co(HDMG)_2]$ in presence of optically active bases, benzil could be reduced to benzoin (equation 54) in an optical yield of 78%. Quinine or quinidine were the chiral bases employed. The best optical yields were obtained with quinine (**60**). It was found that when benzylamine was also present, the rate of hydrogenation was greatly enhanced without any decrease in the optical yield.[276]

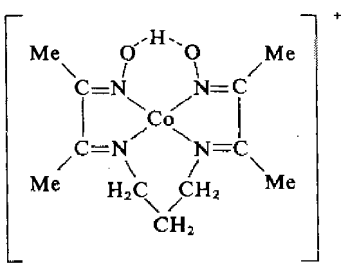


(54)

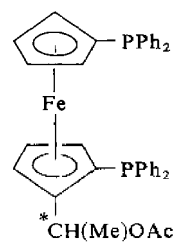
Using a quadridentate ligand derived from 1,3-propanediamine and 2,3-butanedione the cobalt-oxime complex (**61**) was prepared, and again in presence of the chiral base quinine (**60**) this was used to hydrogenate benzil according to equation (54) in an optical yield of 79%.[277] These cobalt systems permitted only low turnover numbers to be achieved.



(**60**)



(**61**)



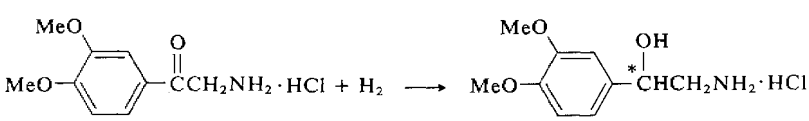
(**62**) BPPFOH

Kumada and co-workers have introduced the ferrocene-based ligand BPPFOH (**62**) for the rhodium-catalyzed asymmetric hydrogenation of carbonyl compounds.

In presence of a stoichiometric quantity of triethylamine, pyruvic acid was hydrogenated by the complex $[Rh(cod)(BPPFOH)]^+$ in an optical yield of 83% to lactic acid (equation 55).[278] The same ligand has been used to hydrogenate aryl aminoalkyl ketones with optical yields of up to 89% (equation 56).[279]

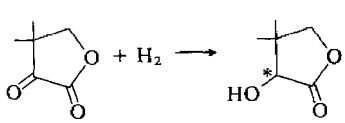


(55)



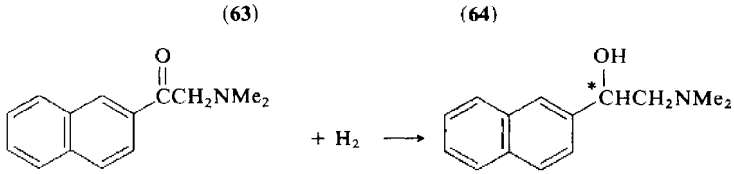
(56)

The α-ketolactone (**63**) can be hydrogenated to give pantolactone (**64**; equation 57). Using $[RhCl(cod)]_2$ and the ligand BPPM (Table 5) an enantiomer excess of 81% was obtained. Related ligands possessing different substituents on the nitrogen atom of BPPM were less effective.[280] When a neutral chloro complex of BPPM was employed as catalyst, the optical yield was raised to 87%.[281] With DIOP (**49**) the best result was only 40%.



(57)

(**63**) (**64**)



(58)

$[RhCl(nbd)]_2$ and DIOP gave an optical yield of 95% in the hydrogenation of α-diethylamino-2-acetonaphthalene (equation 58).[282] This is the highest optical yield yet reported for the asymmetric

hydrogenation of a carbonyl group. There has so far been no really detailed study of the mechanism of these asymmetric hydrogenations and the origin of the optical selectivity remains unknown.

61.2.4 HYDROFORMYLATION

61.2.4.1 Introduction

The hydroformylation reaction is of particular interest here as it involves the activation of two or even three small molecules (equation 59). Isomer formation is quite general where the structure of the alkene permits this and much effort has been invested in attempts to improve the ratio of normal to branched products.

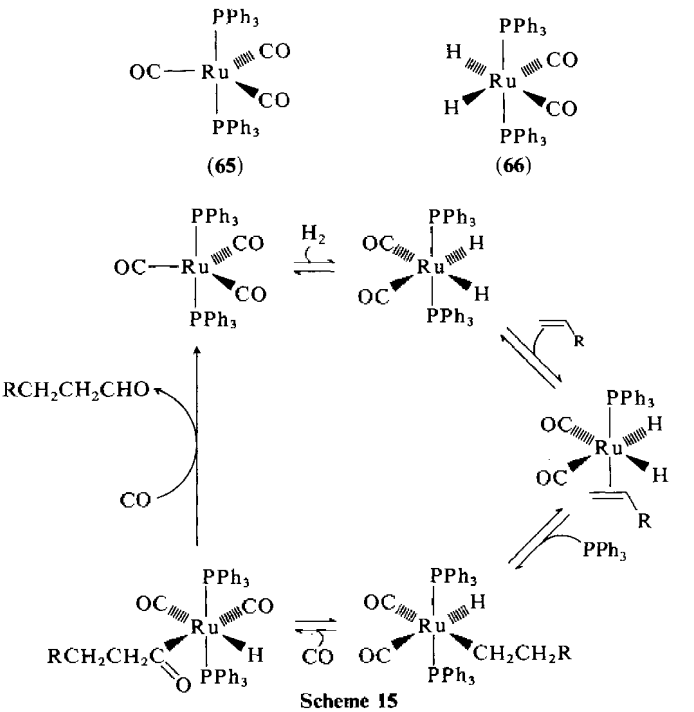
$$CH_3{-}CH{=}CH_2 + H_2 + CO \rightarrow CH_3{-}CH_2{-}CH_2{-}CHO \text{ or } CH_3{-}\underset{\displaystyle CHO}{\underset{|}{CH}}{-}CH_3 \qquad (59)$$

Since its discovery some 50 years ago by Roelen, a great deal of research has been carried out on the reaction and its industrial importance is great. The initial work used as catalyst precursor $[Co_2(CO)_8]$ or simple cobalt salts which were carbonylated under the reaction conditions. Subsequently, phosphine-modified cobalt catalysts were introduced and, more recently, rhodium and platinum catalysts. Only the cobalt and rhodium catalysts have found industrial use to date.

Catalysis of hydroformylation by $[Co_2(CO)_8]$ and other binary metal carbonyls is outside the scope of this work. Reviews are available.[283–286]

61.2.4.2 Iron and Ruthenium

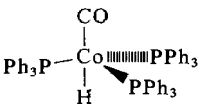
The complexes of these metals show only limited activity as hydroformylation catalysts. $[Fe(CO)_3(PPh_3)_2]$ and related complexes were found to hydroformylate 1-pentene, but the conversion remained low.[287] Its ruthenium analogue $[Ru(CO)_3(PPh_3)_2]$ (**65**) was significantly more efficient.[287–289] $[RuCl_3(PPh_3)MeOH]$ was also active, but $[RuCl_2(PPh_3)_3]$ (**2**) gave very poor conversion and precipitation of the insoluble dicarbonyl $[RuCl_2(CO)_2(PPh_3)_2]$ (**10**). In a more detailed study of ruthenium complexes in hydroformylation, conversions to aldehydes of more than 80% were obtained using 1-hexene as substrate with the catalyst precursors $[Ru(CO)_3(PPh_3)_2]$ (**65**), $[Ru(H)_2(CO)_2(PPh_3)_2]$ (**66**), $[Ru(H)_2CO(PPh_3)_3]$ (**12**), $[RuH(NO)(PPh_3)_3]$, $[Ru(H)_2(PPh_3)_4]$ (**6**), $[Ru(H)_4(PPh_3)_3]$, $[Ru(O_2CMe)_2(PPh_3)_2]$ (**9**) and $[Ru(O_2CBu^t)_2(PPh_3)_2]$. In all cases, complex (**65**) was recovered from the reaction mixtures.[289] Variation of the phosphorus ligand showed that PPh_3 and $P(OPh)_3$ gave the best results. A mechanism was proposed for the hydroformylation using $[Ru(CO)_3(PPh_3)_2]$ as catalyst (Scheme 15).



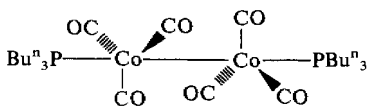
Scheme 15

61.2.4.3 Cobalt

$[Co_2(CO)_8]$ itself as a hydroformylation catalyst lies outside the scope of this article but reviews are available.[283–286] One of the technical problems with this catalyst is the high reaction pressure needed when using it. It was shown by Slaugh *et al.* that hydroformylation could be carried out at very much lower pressure if a phosphine ligand was added to the system. Trialkyl- and mixed alkylaryl-phosphines were used, the latter including the diphosphines $Ph_2P(CH_2)_nPPH_2$ ($n = 2, 4, 5$); $AsBu_3$ and $AsPhEt_2$ were also effective. The best ligand was PBu^n_3.[290] $[Co_2(CO)_8]$ reacts with PBu^n_3 to give the complex $[Co(CO)_3(PBu^n_3)_2]^+$ $[Co(CO)_4]^-$ (**67**). Under hydrogen, $[CoH(CO)_3PBu^n_3]$ (**68**) is formed. This system is more strongly reducing than $[Co_2(CO)_8]$ alone and it facilitates the direct production of alcohols by hydrogenation of the aldehydes formed. Some loss of alkene by hydrogenation occurs. The PBu^n_3-containing catalyst system also exhibits a stronger preference for terminal alkenes than does $[Co_2(CO)_8]$.[290]



(68)



(69)

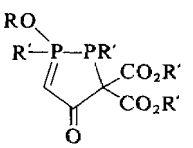
The reactions are solvent dependent. Non-polar solvents favour the formation of the neutral hydride (**68**), whereas in polar media, ionic species predominate. Hydroformylation activity for propylene was observed only under conditions where (**68**) was formed.[291] The dinuclear species $[Co_2(CO)_6(PBu^n_3)_2]$ (**69**) also appears to be catalytically inactive.[290,291] If PBu^n_3 is added in excess over cobalt, only complexes (**68**) and (**69**) were present. The rate of hydroformylation then became first order in hydrogen, owing to the equilibrium shown in equation (60).[292]

$$[Co(CO)_3PBu^n_3]_2 + H_2 \rightleftharpoons 2[CoH(CO)_3PBu^n_3] \quad (60)$$

(**69**) (**68**)

The kinetics of the interconversion of complexes (**67**) and (**68**) have also been studied.[293] It seems that the mechanism of hydroformylation in the presence of PBu^n_3 is similar to that for $[Co_2(CO)_8]$ alone.[285,294]

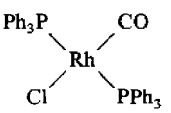
The use of diphosphine ligands, especially diphos itself, together with $[Co_2(CO)_8]$ can lead to catalysts which show significantly improved hydroformylation activity, but as yet nothing is known of the complexes which are formed.[295] Extremely stable and highly selective catalysts were obtained from $[Co_2(CO)_8]$ and derivatives of the ligand 1,2-diphosphacyclopent-5-en-4-one (**70**). Again, nothing is known of the coordination chemistry involved.[296]



(**70**) R = aryl
R' = alkyl

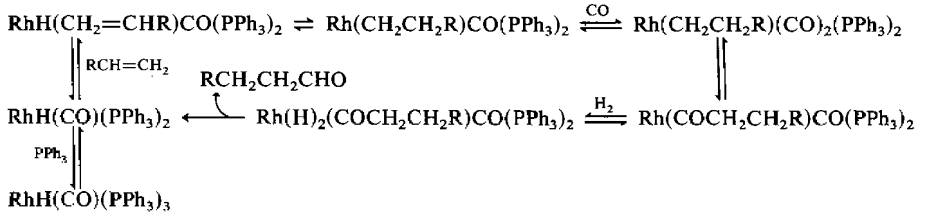
61.2.4.4 Rhodium and Iridium

Wilkinson and co-workers showed that the hydrogenation catalyst $[RhCl(PPh_3)_3]$ (**23**) was also an effective catalyst for the hydroformylation reaction.[297] The complex reacts rapidly with CO to give $[RhCl(CO)(PPh_3)_2]$ (**71**). Both complex (**71**) and a range of its derivatives having other phosphine ligands were shown to catalyze the hydroformylation of 1-pentene under conditions far milder than those needed when $[Co_2(CO)_8]$ was used.[287] In the presence of excess PPh_3 the complex $[RhH(CO)(PPh_3)_3]$ (**34**) was isolated, and this was found to be a better catalyst precursor



(71)

than (**23**) or (**71**). With this complex, alkenes could be hydroformylated rapidly at room temperature and pressure. Terminal alkenes again reacted more rapidly than internal alkenes.[298] Complex (**34**) in the presence of CO gives in solution the species $[RhH(CO)_2(PPh_3)_2]$ (**72**).[299] The mechanism of the hydroformylation is given in Scheme 16.[300]



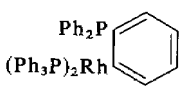
Scheme 16

A most important discovery was that the addition of a large excess of PPh_3 relative to rhodium leads to a very high normal/branched aldehyde ratio, especially when PPh_3 itself is used as solvent.[298] This was attributed to steric effects on the alkene insertion, the excess of PPh_3 preventing its dissociation in this step.

When $P(OPh)_3$ was used as ligand, the effect of an excess of it on the isomer ratio was far less significant.[301] These studies have led to the introduction of an industrial process for the rhodium-catalyzed hydroformylation of propylene to *n*-butyraldehyde which is rapidly gaining in importance relative to the older, cobalt-catalyzed route.[302,303] The relative merits of the two processes have been discussed.[303,304]

It has been found that in the rhodium-catalyzed process a slow loss of catalytic activity occurs and this is partly due to the presence of the more basic PPh_2Pr^n, formed according to equation (61) and involving *ortho*-metallated rhodium intermediates such as (**73**).[305]

$$PPh_3 + CO + H_2 + C_3H_6 \xrightarrow{(Rh)} PPh_2Pr^n + PhCHO \qquad (61)$$



(**73**)

A kinetic study of the hydroformylation has been carried out[306] and the mechanism proposed by Wilkinson (Scheme 16) was extended to express both the associative and dissociative modes of alkene coordination[298] and the formation of *n*- and iso-butyraldehydes. High-pressure IR spectroscopy using CO and either H_2 or D_2 has confirmed the formation of $[RhH(CO)_2(PPh_3)_2]$ in these reactions.[307]

The hydroformylation of (*E*)- and (*Z*)-3-methyl-2-pentene with $[RhH(CO)(PPh_3)_3]$ (**34**) was investigated to clarify the stereochemistry of the reaction. By use of D_2 it was shown that the addition of the H and CHO groups to the alkene occurred with high selectivity in a *cis* manner.[308] Some further reports of hydroformylation catalyzed by complex (**34**) are collected in Table 6.

Table 6 Alkene Hydroformylations Catalyzed by $[RhH(CO)(PPh_3)_3]$

Alkenes	*Ref.*
1-Hexene	309, 310
n-Dodecenes	311
Cycloheptatriene	312
Conjugated dienes	313
1,6-Dienes	314
3,3,3-Trifluoropropene	315
Pentafluorostyrene	315
para-Substituted styrenes	316
Methyl methacrylate	317
Unsaturated acids and esters	318, 319
Diallylamines	320
Bis(alkenyl)carbamates	320

Analogues of $[RhH(CO)(PPh_3)_3]$ with other phosphorus ligands also act as hydroformylation catalysts. Using complex (**34**) in the presence of 1,1′-bis(diphenylphosphino)ferrocene as ligand,

the mechanism of the hydroformylation of 1-hexene was believed to differ from that when only PPh_3 was used, and dinuclear species were postulated.[321] The effect of the diphosphines $Ph_2P(CH_2)_nPPh_2$ ($n = 2$–4) on the hydroformylation of terminal alkenes has been studied.[322–324] Various other 1,4-bis(diphenylphosphino)butane derivatives were also used.[325] The effects on rate and on selectivity to the various aldehyde isomers were complex, and little is known of the coordination chemistry involved other than the obvious implication of chelation.

Following the work of Wilkinson, the complex $[RhCl(CO)(PPh_3)_2]$ (**71**) and its derivatives with other phosphorus ligands have been studied as catalysts for hydroformylation. These reactions quite generally require significantly higher temperature and pressure than those catalyzed by $[RhH(CO)(PPh_3)_3]$. Complex (**71**) has found use in connection with the synthesis of α-hydroxyaldehydes and succinnaldehyde monoacetals.[328] In high-pressure IR work on the hydroformylation of 1-hexene and cyclohexene, it was shown that a small amount of cyclohexenyl peroxide greatly accelerated the reaction. This was due to the conversion of (**71**) to the dicarbonyl $[RhCl(CO)_2PPh_3]$.[329]

The effect of replacing PPh_3 in complex (**71**) by phosphorus ligands having long alkyl chains has been studied using the phosphines PBu^n_3, $P(n\text{-}C_8H_{17})_3$, $P(n\text{-}C_{16}H_{33})_3$, $P(p\text{-}C_6H_4Et)_3$, $P(p\text{-}C_6H_4Bu)_3$ and $P(p\text{-}C_6H_4C_5H_{11})_3$. The trialkylphosphines promote alkene isomerization relative to PPh_3. The substituted arylphosphines, however, gave better ratios of linear/branched aldehydes, with $P(p\text{-}C_6H_4Bu)_3$ giving the most satisfactory combination of yield and selectivity.[330] With 3-phenylpropylene as substrate, rhodium-catalyzed hydroformylation in the presence of the Group V ligands XPh_3 (X = N, P, As, Sb, Bi) was studied at high pressure of H_2 and CO. NPh_3 and PPh_3 gave complete conversions to aldehydes, with the distribution of the three possible aldehydes being the same in each case. With $AsPh_3$ and $SbPh_3$ the conversion began to decrease and 2-phenyl-*n*-butyraldehyde was hardly formed, though the other two aldehydes were again formed in similar proportions. With $BiPh_3$, hydroformylation did not occur.[331]

Complexes containing aminophosphine ligands of the type $[RhCl(CO)L_2]$ (L = PPh_2NEt_2, $PPh(NEt_2)_2$, $P(NEt_3)_3$, PPh_2NMe_2, $PPh(NMe_2)_2$, $PPh_2N(Me)Cy$, $PPh\{N(Me)Cy\}_2$ and $\{PPh_2N(Me)CH_2\}_2$) have been studied as catalysts for the hydroformylation of 1-hexene.[332] These ligands all have basicities lying between those of PPh_3 and PBu_3. IR and ESCA studies showed the aminophosphines in these complexes must be considered as electron acceptor ligands, the order of electron affinity being $N(Me)Cy > NEt_2 > NMe_2$. The electron density on phosphorus and nitrogen increased as the number of phenyl groups in the ligand decreased. In the free ligands, electron donation from nitrogen to phosphorus occurred, whereas in the rhodium complexes it was in the reverse direction.

Both the conversion to aldehydes and the selectivity to normal aldehydes observed in the hydroformylation of 1-hexene by these complexes were markedly ligand dependent. A linear relationship between the electron density on the nitrogen atom and the normal/branched aldehyde ratio was found, indicating that for these aminophosphines the ratio is largely controlled by electronic factors.[332]

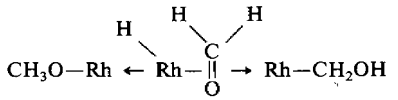
By ligand exchange in $[RhCl(CO)(PPh_3)_2]$ (**71**), or by direct reaction of the phosphine ligand with $[Rh_2Cl_2(CO)_4]$, a series of silicon-containing phosphine complexes were prepared.[333] The latter reaction in presence of LiI gave the corresponding iodides. The complexes obtained in this way were $[RhX(CO)(PPh_2CH_2SiMe_3)_2]$ (X = Cl, I), $[RhI(CO)(PPh_2CH_2CH_2CH_2SiMe_3)_2]$ and $[RhX(CO)\{PPh_2CH(Me)Si(OSiMe_2)_3O\}_2]$ (X = Cl, I). $[RhCl(CO)(PPh_2CH_2SiMe_3)_2]$ gave very similar behaviour to complex (**71**) in the hydroformylation of 1-hexene, but the iodo complexes gave both lower conversions to aldehydes and much poorer selectivities to *n*-heptanal. $[RhI(CO)(PPh_2CH_2SiMe_3)_2]$ gave branched aldehyde as the major product.[333]

The hydroformylation of methyl acrylate, methyl methacrylate, methyl crotonate and methyl tiglate has been studied with reference to the selectivity for introduction of the formyl group at the α- or β-carbon atom. The catalysts used were prepared *in situ* from $[Rh_2Cl_2(CO)_4]$ and $Ph_2P(CH_2)_nPPh_2$ ($n = 2$–5), $Cy_2P(CH_2)_nPCy_2$ ($n = 2$–4) and $DBP'(CH_2)_2DBP'$ (DBP' = 5*H*-dibenzophospholyl).[334] Good selectivity to α-formyl derivatives was obtained only with those ligands having $n = 2$–4. The dibenzophosphole group was also shown to cause significant rate enhancement in alkene hydroformylation.[335]

In addition to C=C bonds, $[RhCl(CO)(PPh_3)_2]$ (**71**) has been shown to catalyze the hydroformylation of formaldehyde to give glycol aldehyde (equation 62).[336] Small amounts of methanol were obtained as a by-product. The reaction requires *N,N*-dialkylamides as solvents, otherwise methanol is the major product and no glycol aldehyde is formed. Coordinated amide solvent was thought

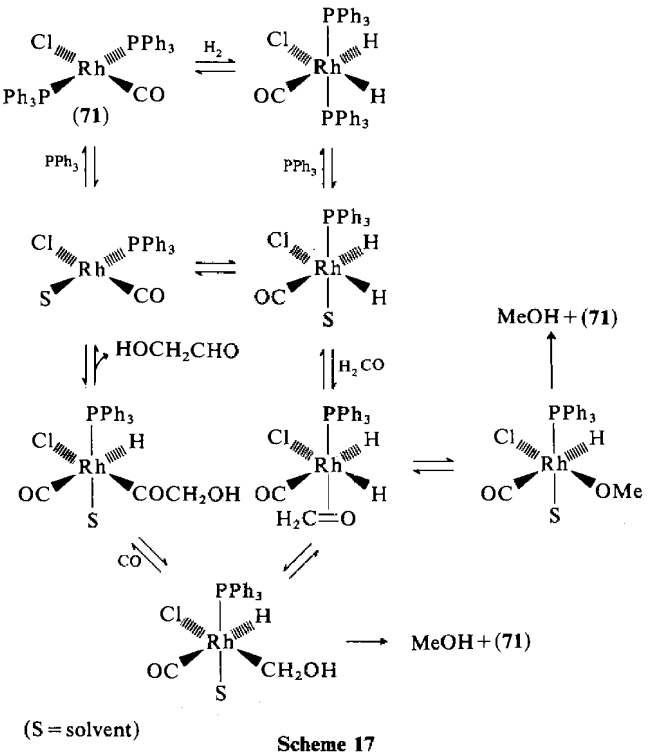
$$H_2C{=}O + H_2 + CO \rightarrow HOCH_2CHO \qquad (62)$$

to direct the formaldehyde insertion step towards formation of a hydroxymethyl rather than a methoxy intermediate (equation 63).



(63)

A large number of rhodium complexes having different anions and phosphorus ligands were studied, but complex (**71**) was the best catalyst, being under these conditions somewhat surprisingly better than $[RhH(CO)(PPh_3)_3]$. The mechanism proposed for the reaction is shown in Scheme 17. Deuteration studies showed that the distribution of deuterium in the glycol aldehyde was consistent with this mechanism.[336] It has been shown that, in presence of small amounts of an amine, the reaction can be carried out in solvents other than dialkylamides.[337] The amines also significantly increased the reaction rate.

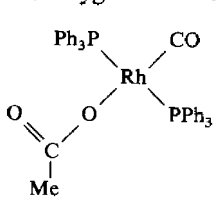


(S = solvent)

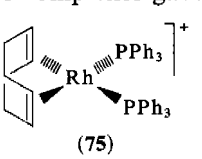
Scheme 17

Complexes of carbonic or carboxylic acid anions have been used as hydroformylation catalysts for various alkenes. The bicarbonate complex $[Rh(H)_2(O_2COH)(PPr^i_3)_2]$ as catalyst enabled 1-hexene to be converted to aldehydes using paraformaldehyde as source of hydrogen and carbon monoxide in place of the more usual gas mixture.[338] The acetate complex $[Rh(OAc)CO(PPh_3)_2]$ (**74**) has been shown to effect the selective hydroformylation of cyclic dienes. The cyclohexadienes gave predominantly dialdehydes, whereas 1,3- and 1,5-cyclooctadiene gave the saturated monoaldehydes.[339]

Propylene hydroformylation was catalyzed by $[Rh(O_2C\text{-}n\text{-}C_5H_{11})CO(PPh_3)_2]$, which is the caproyl analogue of (**74**).[340] In the hydroformylation of alkenes with $[Rh_4(CO)_{12}]$, complexes of the type $[Rh(O_2CR)(CO)_2]_2$ were isolated from the reaction mixture. As the R groups always corresponded to the alkene used, their presence was attributed to oxidation of rhodium-acyl intermediates by extraneous oxygen.[341] With PPh_3 these complexes gave analogues of (**74**).



(**74**)

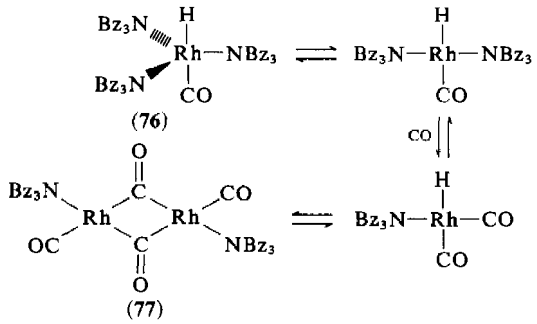


(**75**)

Diene complexes have been used as precursors for hydroformylation catalysts. $[RhCl(nbd)]_2$ in presence of PPh_3 was used in a kinetic study of the hydroformylation of 1-heptene.[342] Cationic diene complexes of the type $[Rh(cod)(XPh_3)_2]^+$ (X = N, P, As, Sb, Bi) having a non-coordinating anion (ClO_4^-) were employed in the hydroformylation of 1-heptene. The performances of the different ligands were surprisingly similar as regards conversion and selectivity even when large excesses of the ligands were used.[343] $[Rh(cod)(PPh_3)_2]^+$ (**75**) hydroformylates 1-hexene at normal temperature and pressure in presence of Et_3N but isomerization of the alkene is extensive. In presence of PPh_3, $[RhH(CO)(PPh_3)_3]$ (**34**) was isolated in good yield from these reactions. $[Rh(cod)py(PPh_3)]^+$ was much less effective than (**75**). $[Rh(cod)_2]^+$ was inactive unless PPh_3 was added.[344]

The complex $[RhH(CO)(mSPPh_2)_3]$ containing the water-soluble phosphine $mSPPh_2$ (**31**) has also been prepared, and it was shown to hydroformylate 1-hexene in the pH range 5.2–9.2.[345]

$[RhH(CO)(NBz_3)_3]$ (**76**) also hydroformylates terminal alkenes at normal temperature and pressure. In solution under an atmosphere of H_2 and CO, dissociation of NBz_3 and formation of a dinuclear species (**77**) occur (Scheme 18).[346] Using 1-octene as substrate it was found that *n*-nonanal was the predominant aldehyde formed, but extensive alkene isomerization occurred.[346]



Scheme 18

The complex $[Rh(nbd)(amphos)_2]^{3+}$, which contains the water-soluble ligand amphos (**33**), has been prepared. In a two-phase system this complex acted as a hydroformylation catalyst for 1-hexene.[133] Isomerization of the alkene occurred to a limited extent. In the presence of H_2 and CO the dicarbonyl $[Rh(CO)_2(amphos)_2]^{3+}$ was thought to be formed.

The tris(2-pyridyl)phosphine complex $[RhH(CO)(PPh_3)(Ppy_3)_2]$ in the presence of an excess of the pyridylphosphine ligand has been shown to hydroformylate 1-hexene. A high selectivity towards 1-hexene was achieved.[347]

Iridium complexes show very limited activity as hydroformylation catalysts compared with those of rhodium. $[IrCl(CO)(PPh_3)_2]$ (**43**) has been shown to hydroformylate terminal alkenes but much higher temperature and pressure are required than with rhodium.[348,349] Reviews on rhodium-catalyzed hydroformylation are available.[350,351]

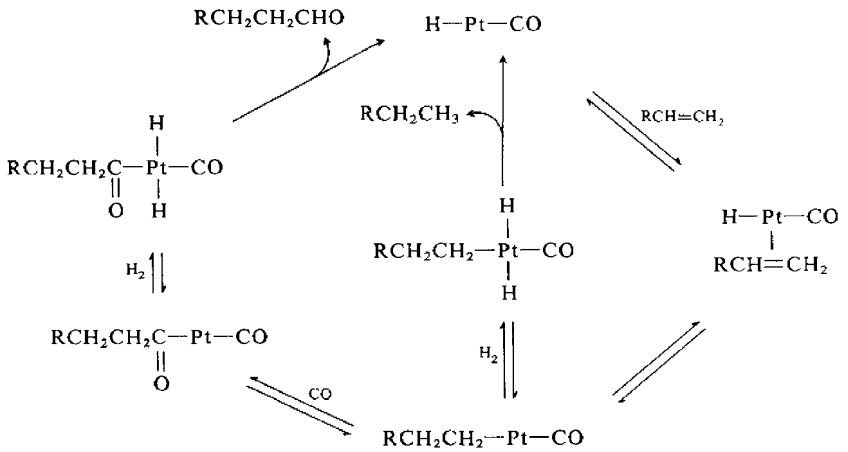
61.2.4.5 Platinum

In presence of $SnCl_2$, platinum complexes are effective hydroformylation catalysts. For terminal alkenes they generally give much higher selectivity to normal aldehydes than do cobalt or rhodium catalysts. $[PtH(SnCl_3)CO(PPh_3)_2]$ (**78**) at high temperature and pressure converted 1-pentene to *n*-hexenal. $[PtH(SnCl_3)(PPh_3)_2]$ (**48**) and $[PtH(Cl)(PPh_3)_2]$ (**79**) in presence of $SnCl_2$ were also active catalysts. In all three cases, (**78**) was recovered from the reaction mixtures after hydroformylation. Using (**78**) as catalyst the rate of the reaction was five times higher than with $[Co_2(CO)_8]$ under the same conditions and the selectivity to normal aldehydes was also higher.[352] Complex (**78**) may have the four-coordinate structure $[PtH(CO)(PPh_3)_2]^+ SnCl_3^-$.

The use of $[PtCl_2(PPh_3)_2]$ (**80**) in presence in $SnCl_2$ and other main group metal halides as catalysts for hydroformylation has been studied in detail.[353] In absence of $SnCl_2$, (**80**) gave no significant conversion of 1-heptene to aldehydes. Both $SnCl_4$ and $GeCl_2$ with complex (**80**) led to hydroformylation but they were much less effective than $SnCl_2$; $PbCl_2$, $SiCl_4$ and $SbCl_3$ were also ineffective. Other tin halides and various phosphine, arsine and stibine ligands were investigated, but the best yield of *n*-octanal was obtained with the $[PtCl_2(PPh_3)_2]$–$SnCl_2$ combination. The preferred Sn/Pt ratio was about five. The order of reactivity of different alkenes was similar

to that observed with rhodium and cobalt catalysts, terminal straight-chain alkenes giving the best results.

It was believed that $[PtH(SnCl_3)CO(PPh_3)]$ was the active species formed in these reactions. The basics of the proposed mechanism are given in Scheme 19; $SnCl_3^-$ and PPh_3 ligands are not included. Chloride was thought not to be present in view of the excess of $SnCl_2$. Isomerization can occur by reversal of the alkene insertion, as usual. The probable oxidation states of the various platinum complexes involved were not discussed, nor was the mode of hydrogen activation.[353]

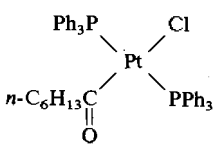


Scheme 19

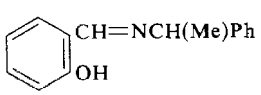
The use of an appropriate chelating diphosphine ligand greatly enhances the catalytic activity observed with the $[PtCl_2(PPh_3)_2]$-$SnCl_2$ system.[354] For diphosphines of the type $Ph_2P(CH_2)_nPPh_2$ ($n = 1$–6, 10) the activity reached a maximum at $n = 4$, this system being roughly four times as active as those with $n = 3$, 5 or 6. For $n = 1$, 2 or 10 the activity was minimal in comparison; the alkene used was 1-pentene. By restricting the mobility of the alkene chain of the phosphine, even better selectivity to normal aldehyde could be achieved. Using the cyclobutane derivative (**55**) the selectivity to *n*-hexenal was 99%. This required only one mole of (**55**) per mole of platinum, whereas in the $[RhH(CO)(PPh_3)_3]$-catalyzed reactions very large excesses of PPh_3 are needed to attain a selectivity of *ca.* 94% (see Section 61.2.4.4). The strong dependence on the size of the chelate ring was interpreted as being due to the need for the phosphine to function as both a bidentate and a monodentate ligand at differing points in the catalytic cycle.[354]

The carbonyl complexes $[PtCl_2(CO)(XR_3)]$ (X = P, As; R = aryl, alkyl) in presence of $SnCl_2$ all catalyzed the hydroformylation of 1-hexene with good selectivity to *n*-heptanal.[355] It has been shown that the high selectivity towards normal aldehydes exhibited in platinum-catalyzed hydroformylation can be used to produce terminal (*i.e.* normal) aldehydes from internal alkenes. With the cationic complex $[PtCl(CO)\{P(OPh)_3\}_2]^+$, again in presence of $SnCl_2$, *trans*-5-decene gave up to 17% *n*-undecanal; with $[PtCl(CO)(PPh_3)_2]^+$ (**81**) in presence of $ZnBr_2$ a linearity of 62% was achieved, though at reduced conversion.[356]

From the reaction of *cis*-$[PtCl_2(PPh_3)_2]$ with 1-hexene and CO under pressure in ethanol, the complex $[PtCl(CO\text{-}n\text{-}C_6H_{13})(PPh_3)_2]$ (**82**) has been isolated. In the presence of $SnCl_2$ it catalyzes the hydroformylation of 1-hexene. The crystal structure of (**82**) was determined: the complex is approximately square planar, and is the *trans* isomer; no unusual features were present in the structure. It is interesting that the free chloro complex was obtained although more than a threefold excess of $SnCl_2$ was present in the preparation of (**82**).[357] The complex $[Pt(SnCl_3)(COPr^n)(PPh_3)_2]$ has also been isolated; it is believed that a platinum–tin bond is present in the complexes taking part in the catalytic cycle.[358]



(**82**)



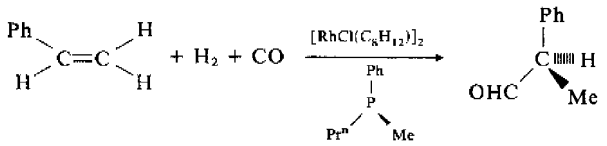
(**83**)

The high selectivity shown by the platinum–tin catalysts and the importance of the industrial synthesis of normal aldehydes suggests that further study will be most rewarding. A review on hydroformylation by the platinum metals is available.[359]

61.2.4.6 Asymmetric Hydroformylation

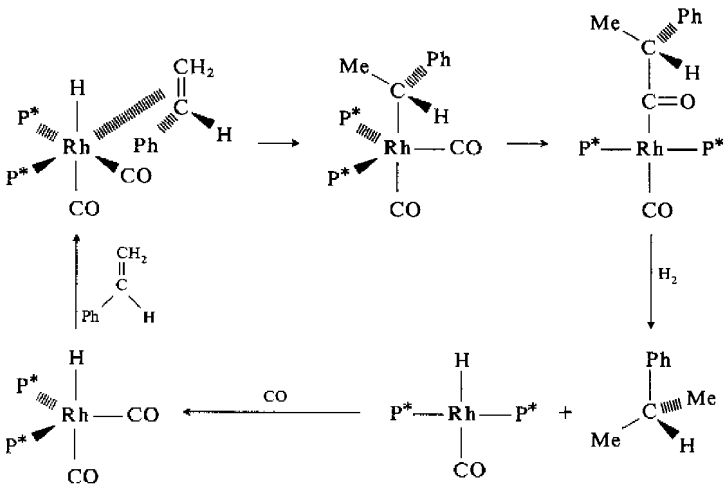
Using $[Co_2(CO)_8]$ in the presence of the (*S*)-form of the ligand *N*-α-methylbenzylsalicylaldimine (**83**) as catalyst in ethanolic solution, styrene gave 2-phenylpropanal as its diethyl acetal with an optical purity of 15%.[360]

More successful attempts at asymmetric hydroformylation have involved rhodium and platinum complexes. As in asymmetric hydrogenation, best results have been obtained with optically active chelating diphosphines as ligands, but some studies of monophosphines have been made. Using



(64)

(*S*)-(+)-methyl(*n*-propyl)phenylphosphine and $[RhCl(C_8H_{12})]_2$) styrene gave (*R*)-(−)-2-phenylpropanal in an optical purity of 20–30% (equation 64). The mechanism shown in Scheme 20 was proposed for the reaction.[361]



Scheme 20

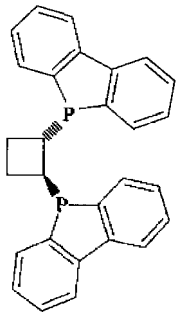
With $[Rh_2Cl_2(CO)_4]$ as catalyst precursor, together with (*R*)-benzyl(methyl)phenylphosphine or neomenthyldiphenylphosphine, styrene was hydroformylated to 2- and 3-phenylpropanal (equation 65); 2-phenylpropanal was the major product. The optical yields were not given, but

$$PhCH{=}CH_2 + H_2 + CO \rightarrow Ph{-}\underset{\displaystyle CHO}{\underset{|}{CH}}{-}CH_3 + PhCH_2CH_2CHO \qquad (65)$$

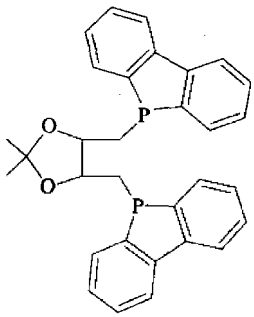
the observed optical rotations showed that benzyl(methyl)phenylphosphine was several times more effective than the neomenthyl derivative.[362] In a related study of the asymmetric hydroformylation of styrene, $[Rh_2Cl_2(CO)_4]$ gave 2-phenylpropanal with optical purities of 17.5 and 21% using as ligands (+)-benzyl(methyl)phenylphosphine and (−)-methyl(*n*-propyl)phenylphosphine respectively. Neomenthyldiphenylphosphine gave an optical yield of less than 1%. Using $[RhH(CO)(PPh_3)_3]$ (**34**) in the presence of DIOP (**49**) the optical purity was 23%. Simple aliphatic alkenes were also studied using (**34**) and (**49**) and *cis*-2-butene gave 2-methylbutanal in an optical yield of 27% as the best result.[360] With $[Rh_4(CO)_{12}]$ and the chelating bis(dibenzophospholyl) ligand (**84**) at a phosphorus/rhodium ratio of 4, styrene gave 2-phenylpropanal in an optical yield of 40%. Both 1- and 2-butenes and 2-phenylpropylene lead to significantly poorer results.[363]

N-Vinylsuccinnimide and *N*-vinylphthalimide were hydroformylated using complex (**34**) and the ligands DIOP (**49**), DIPAMP (**50**) and DIPHOL (**85**). Optical yields for the resulting 2-imidopropanals of up to 27% for the succinnimide and 38% for the phthalimide derivatives could be obtained, in both cases with (**85**) as ligand.[364]

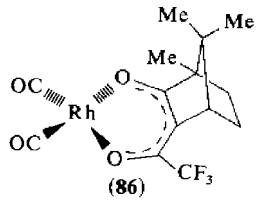
An attempt to use the 3-trifluoro-1*R*-camphorate complex (**86**) as a catalyst for the asymmetric hydroformylation of styrene failed as the ligand dissociated rapidly under the reaction conditions.[365]



(**84**)



(**85**) DIPHOL



(**86**)

The majority of studies of asymmetric hydroformylation with rhodium and platinum complexes have made use of DIOP (**49**) as a ligand. With either the complex [RhCl(CO)(DIOP)] or $[RhCl(C_2H_4)_2]_2$ plus DIOP, styrene was hydroformylated to 2-phenylpropanal with optical yields of only 16%.[366] When α-monodeuterostyrene was used as substrate, with DIOP and complex (**34**) as catalyst, essentially the same optical yield was obtained.[367] The same catalyst with non-deuterated styrene under different conditions gave an optical yield of 25%.[368]

In diene hydroformylation with complex (**34**) and DIOP, the attainable optical yields were critically dependent on the diene. Thus isoprene gave, after oxidation of the aldehyde with Ag_2O, 3-methylpentanoic acid as major product having an optical purity of 32%. Butadiene, 2,3-dimethylbutadiene and 2-methyl-1-butene all gave optical yields of less than 6%.[369] The hydroformylation by (**34**) and DIOP of a number of alkenes having C_{2v} symmetry gave best results with *cis*-2-butene, with an optical yield of 27%.[370]

$[Rh_2Cl_2(CO)_4]$ together with DIOP, benzyl(methyl)phenylphosphine or neomenthyldiphenylphosphine has been investigated in the hydroformylation of vinyl acetate (equation 66).

$$CH_2{=}CHOCMe + H_2 + CO \rightarrow Me{-}C(OCMe)(H){-}CHO \qquad (66)$$

The monophosphines gave optical yields of 2.1 and 0.5% respectively, but with DIOP a best result of 23% was obtained.[371] The product of this hydroformylation is a potential precursor for the amino acid threonine.

When [Rh(acac)(cod)] was used with DIOP as ligand, a best optical yield of 40% was achieved. With the related ligand DIPHOL (**85**) the optical yield was raised to 51%. The chemical yields of the 2-acetoxypropanal were in the range 75–95%.[372]

The complex $[PtCl_2(DIOP)]$ in the presence of $SnCl_2$ has been used as catalyst for the asymmetric hydroformylation of various alkenes. With a series of butene and styrene derivatives very low optical yields were obtained. The best results were achieved with 2,3-dimethyl-1-butene which gave 15% optically pure 3,4-dimethylpentanal, and with α-ethylstyrene which gave 15% optically pure 3-phenylpentanoic acid after oxidation of the aldehyde.[373]

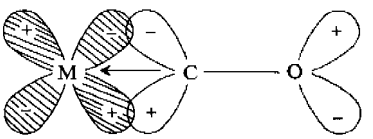
Using D_2 and CO, with $[PtCl(SnCl_3)(DIOP)]$ as catalyst, (*Z*)- and (*E*)-2-butene were converted to *erythro*- and *threo*-1,3-$[^2H]_2$-2-methylbutanal respectively with high selectivity. This indicates that the H and CO groups are added in a *cis* manner to the double bond, as is the case with $[RhH(CO)(PPh_3)_3]$ (**34**).[374] Using $[PtCl_2(DIOP)]$-$SnCl_2$ or the DIPHOL (**85**) analogue, it was shown that a given enantiomer of the ligand gave different enantiomers of the resulting 2-methylbutanal when starting with (*Z*)- or (*E*)-2-butene,[375] contrary to a previous report.[373] Here again, the behaviour is the same as for the rhodium catalyst.

That very high optical yields can be obtained in asymmetric hydroformylation has now been demonstrated. Using $[PtCl_2(-)\text{-}(DIOP)]$ and $SnCl_2$ in benzene solution, careful choice of the reaction conditions permitted the conversion of styrene to (+)-2-phenylpropanal in an optical yield of 95%.[376] With DIOP the best result was 35%. Even slight variation of the reaction conditions caused the optical yield obtained with DIPHOL to fall significantly, indicating clearly that to obtain the best possible results in asymmetric catalysis, *all* reaction parameters must be optimized.

61.2.5 CARBONYLATION

61.2.5.1 Introduction

Whilst the number of carbonyl ligand-containing complexes known today is vast, only relatively few have been shown to take part in homogeneously catalyzed reactions. Coordination and activation are therefore not synonymous. The bonding involves donation from the carbon lone pair to an empty metal orbital, and back donation from a filled metal *d*-orbital to an empty antibonding π^*-orbital of the carbonyl ligand (**87**).



(**87**)

The relative extent of this σ-donation and π-acceptor behaviour determines the electron density in the neighbourhood of the carbon atom and consequently its reactivity. This electron density is further very dependent on the transition metal, its oxidation state and the other ligands in its coordination sphere. The frequency of the CO stretching vibration in the IR spectrum gives an indication of the resulting electron distribution.[377] The higher this frequency the more positive is the carbon atom and the greater is its susceptibility to nucleophilic attack.[378] Unfortunately, the carbonyl intermediates occurring in catalytic carbonylations are rarely amenable to IR study.

The so-called insertion reaction (equation 4) is the most common way in which a new bond to the carbonyl carbon atom is formed. It should be noted that the reaction is misnamed as a more correct picture involves the migration of the group X to the carbonyl carbon, rather than an insertion of CO into the M—X bond.[379] This may therefore be regarded as a nucleophilic attack on the carbonyl carbon atom and the relevance of it bearing a partial positive charge is apparent. In many carbonyls no significant change in the electron density at the carbon atom occurs, and they are thus not activated by coordination. A review is available on this topic.[380] Carbonylation by binary metal carbonyls is outside the scope of this work and the companion volumes 'Comprehensive Organometallic Chemistry' should be consulted.

61.2.5.2 Ruthenium

The carbonylation of methanol, dimethyl ether and methyl acetate using as catalyst precursors $[RuI_2(CO)_4]$ and $[Ru(acac)_3]$ (**88**) with NaI, HI or MeI as promoter has been reported.[381] The major products were ethanol from methanol, methyl acetate from dimethyl ether, and acetic anhydride plus acetic acid from methyl acetate (equations 67–69).

$$MeOH + CO + 2H_2 \rightarrow EtOH + H_2O \quad (67)$$

$$MeOMe + CO \rightarrow MeC(=O)OMe \quad (68)$$

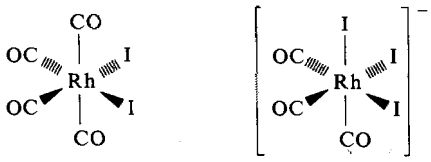
$$MeC(=O)OMe + CO \rightarrow MeC(=O)OC(=O)Me \quad (69)$$

Further carbonylation can occur, adversely affecting the selectivities obtained. Where it is used, the effect of hydrogen pressure on selectivity is also significant, as not all of the reactions require hydrogen. The production of water and the presence of alcohols lead to esterification–hydrolysis equilibria and water can affect the hydrogen pressure *via* the reversible water-gas shift reaction (equation 70).

$$H_2O + CO \rightarrow H_2 + CO_2 \quad (70)$$

Relatively high temperatures and pressures are required for these carbonylations. When complex (**88**) is used as catalyst precursor in presence of an iodide source, two ruthenium(II) complexes have been shown to be formed. They are *cis*-$[RuI_2(CO)_4]$ (**89**) and *fac*-$[RuI_3(CO)_3]^-$ (**90**).

Use of (**88**) requires the presence of hydrogen to reduce it to ruthenium(II). Compounds (**89**) and (**90**) are believed to be in equilibrium with one another under the reaction conditions, and



(89) (90)

complex (**90**) is thought to initiate the catalytic cycle. Hydrogen or a proton source (H_2O, MeOH, HI) is essential. Complex (**90**) or one similar reacts to give a ruthenium methyl species, which then undergoes CO insertion to give an acyl. Reaction of this with hydrogen, water, methanol or iodide could then lead to the various products observed, but the full details of the mechanism remain unknown.

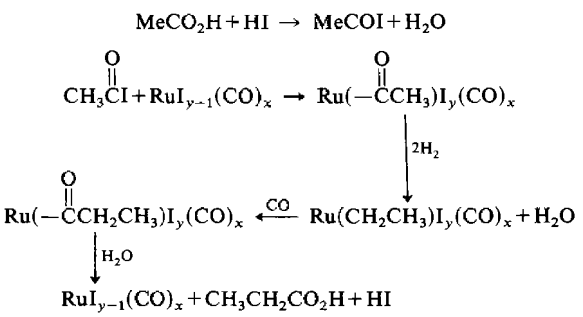
A further reaction of the above type is ester homologation. The production of ethyl acetate from methyl acetate (equation 71) using similar catalytic systems to the above has been studied.[382]

$$MeCOMe + CO + 2H_2 \rightarrow MeCOEt + H_2O \quad (71)$$

Complex (**88**) with an iodide source was again used. The selectivity was surprisingly dependent on the cation of the iodide. It has been found that cobalt(II) acetate improves the conversion and selectivity achieved in equation (71) when used together with complex (**88**) as catalyst.[383] In a related reaction, acetic acid was carbonylated to propionic acid (equation 72).

$$MeCO_2H + 2H_2 + CO \rightarrow EtCO_2H + H_2O \quad (72)$$

The ruthenium source was typically RuO_2, $RuCl_3$, $Ru(acac)_3$, $[Ru_4(H)_4(CO)_{12}]$ or a binary carbonyl, again with a source of iodide present as a promoter;[384,385] MeI, EtI or HI was employed. Both complex (**90**) and $[Ru_2I_2(CO)_6]$ were observed in the reaction mixtures. The reaction gave carboxylic acids of longer chain length than propionic acid. A mechanism was proposed in which the precise nature of the iodocarbonyl complexes was not specified (Scheme 21).

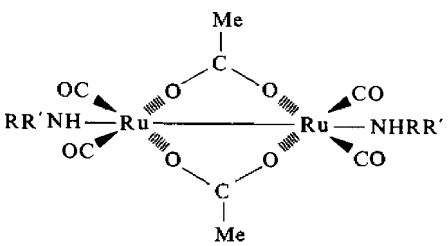


Scheme 21

The polynuclear complex $[Ru(OAc)_2(CO)_2]_n$ (**91**) has been shown to catalyze the carbonylation of secondary amines to formamides at normal pressure and 75 °C (equation 73). Some primary amines also react.[386,387]

$$RR'NH + CO \rightarrow RR'NCHO \quad (73)$$

In amine solution, (**91**) gives dinuclear species $[Ru(OAc)_2(CO)_2(RR'NH)_2]$ (**92**). The carbonylation is autocatalytic, suggesting that these complexes must undergo further reactions before



(92)

becoming catalytically active. The polynuclear hydridocarbonyl complex $[RuH(CO)_3]_n$ when used as catalyst precursor showed no autocatalytic behaviour, and possibly reacts with the amine to enter the catalytic cycle directly.

$[Ru(acac)_3]$ (**88**) has also been used as catalyst precursor for the reduction of CO with H_2.[388] These reactions require very high temperature and pressure. The only products formed by CO reduction were methanol and methyl formate. Complex (**88**) is carbonylated under the reaction conditions and some carbonyl complexes can be used in its place. $[Ru(CO)_5]$ was shown to be formed in all cases in the reaction mixture. The use of acetic acid as solvent promoted the formation of ethylene glycol esters in these reactions.[389] Complex (**91**) was also used and again $[Ru(CO)_5]$ was observed. When iodide was added to the system, the activity and selectivity to the two carbon products ethanol and ethylene glycol increased significantly.[390] Using KI, no $[Ru(CO)_5]$ was detected, but both complex (**90**) and $[Ru_3H(CO)_{11}]^-$ were present. Neither of these complexes when used alone gave more than very limited activity. Optimum performance required a 2:1 ratio of the hydride to (**90**). Using catalyst precursors such as $RuCl_3 \cdot 3H_2O$, $[Ru(acac)_3]$, $[Ru(CO)_3(PPh_3)_2]$ (**65**) and others, the yields and selectivities to C_2 products have been found to be markedly affected by the presence of bulky cations, possibly owing to their effect on the polarity of the medium.[391] Attempts to hydrogenate CO to C_2 products in *n*-propanol solution using $[RuCl_2(PPh_3)_3]$ (**2**), $[Ru(acac)_3]$ (**88**) or $RuCl_3 \cdot 3H_2O$ led only to the formation of propyl formate and propyl acetate.[392]

The water-gas shift reaction (70) is of great importance in adjusting the H_2/CO ratio in synthesis gas mixtures, and attempts have been made to find homogeneous catalysts capable of better performance than the heterogeneous catalysts currently used in industry. In aqueous KOH, $RuCl_3 \cdot 3H_2O$ acts as a catalyst for the reaction at 90 °C and near normal pressure.[393] The porphyrin complex $[Ru(TPPS)CO]^{4-}$ (TPSS = *meso*-tetrakis(4-sulfonatophenyl)porphyrinate) behaves similarly and both gave better results than did $[Ru_3(CO)_{12}]$. The complex $[RuCl(CO)(bipy)_2]^+$ has been shown to catalyze the water-gas shift reaction in both photochemical and thermal reactions.[396] The details of the mechanism are not yet clear, but attack of hydroxide on a carbonyl ligand to give a formate complex is involved.

The complexes $[Ru(cod)py_4]^{2+}$, $[RuCl_2(CO)_2py_2]$ and $[RuCl_2py_4]$ catalyze the reduction of nitrobenzene by carbon monoxide and water (equation 74).[397] The cationic complex gave the best results, and a number of substituted nitrobenzenes were reduced in good yields. Unlike some other catalysts for this reaction, it did not catalyze the water-gas shift (equation 70).

$$PhNO_2 + 3CO + H_2O \rightarrow PhNH_2 + 3CO_2 \quad (74)$$

$$2NO + CO \rightarrow N_2O + CO_2 \quad (75)$$

$[Ru(NO)_2(PPh_3)_2]$ catalyzes the reduction of nitric oxide by carbon monoxide (equation 75).[398]

61.2.5.3 Cobalt

The carbonylation of methanol is an important route to acetic acid and is the basis for two industrial processes (cobalt- and rhodium-catalyzed). The cobalt-catalyzed route uses $[Co_2(CO)_8]$ as catalyst with an iodide promoter, and lies outside the scope of this work. The companion volumes 'Comprehensive Organometallic Chemistry' should be consulted.

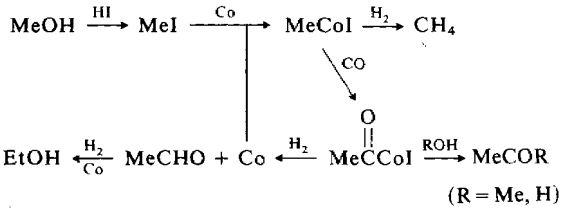
The conversion of methanol to ethanol with carbon monoxide and hydrogen has attracted considerable attention. Further carbonylation to higher alcohols occurs much more slowly, but acetic acid formation is a competing reaction and this leads to ester formation. Using CoI_2 in presence of PBu^n_3 as catalyst, the selectivity to ethanol was improved by addition of the borate ion $B_4O_7^{2-}$.[399] This was attributed to an enhanced carbene-like nature of an intermediate cobalt-acyl complex by formation of a borate ester (equation 76). This would favour hydrogenolysis to



(76)

ethanol rather than hydrolysis to acetic acid. Using CoI_2 and the diphosphines $Ph_2P(CH_2)_nPPh_2$ ($n = 1$–6), selectivities to ethanol of up to 89% were achieved.[400] The reaction sequence given in Scheme 22 was proposed. No further details regarding the nature of the cobalt complexes involved were available. The diphosphines having $n = 2$ or 3 gave the lowest selectivity to ethanol (35–65%). These ligands should form the most stable chelate rings with the metal. For $n = 1$, 4 or 5, the selectivities were of roughly the same order (81–89%). The extent of formation of acetic acid,

methyl acetate and propanol was negligible, but significant quantities of methane were obtained. The high selectivity to ethanol was attributed to the ease of hydrogenation of the acylcobalt intermediate.



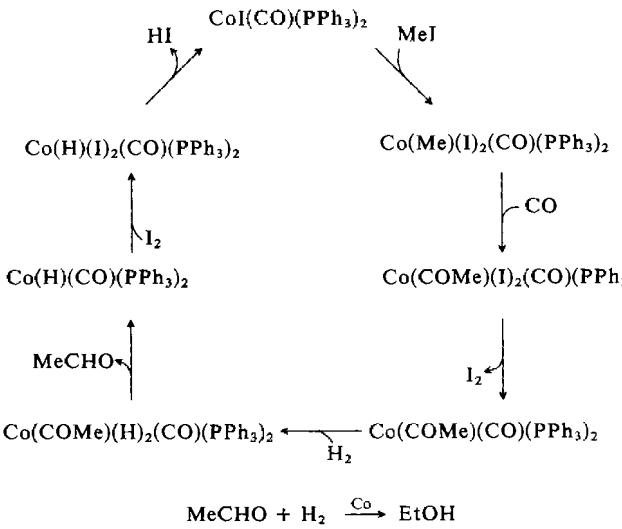
Scheme 22

Using $Co(OAc)_2$ in presence of PPh_3 and HI as catalyst precursor the mechanism of the reaction has been studied.[401] A number of cobalt complexes having I^-, PPh_3 and CO as ligands were also investigated and $[CoI_2(PPh_3)_2]$ gave the best results. When CD_3OD was used, no H/D exchange occurred in the methyl group, ruling out the possibility of carbene formation according to equation

$$MeOH + Co \rightarrow H_2C{=}Co + H_2O \qquad (77)$$

(77). The acyl route (Scheme 22) was accepted and the detailed mechanism given in Scheme 23 was evolved.

$$MeOH + HI \longrightarrow MeI + H_2O \qquad (78)$$



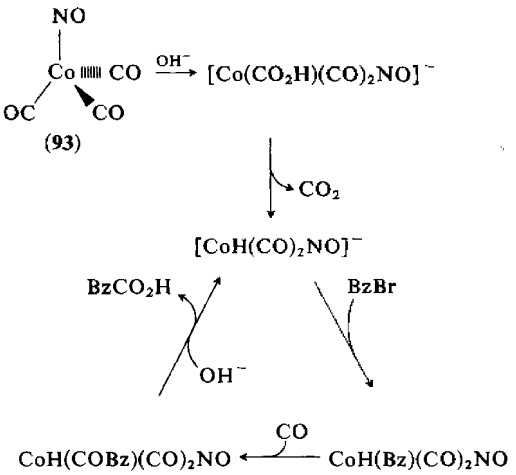
Scheme 23

There remains the question of whether the acyl group can be further reduced without elimination of acetaldehyde, giving ethanol directly. The reductive elimination of iodine is perhaps in need of further substantiation.

Hydrogenation of the acyl complex $[Co(COMe)(CO)_3PPh_2Me]$ gave a product distribution very similar to that obtained when $[Co(CO)_3PPh_2Me]$ was used as a catalyst for methanol homologation.[402] This was regarded as further evidence for the presence of an acyl intermediate in the catalytic reaction.

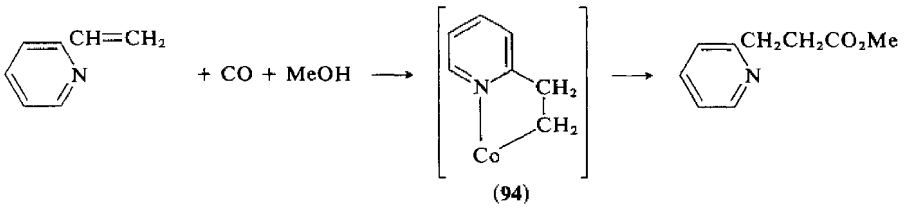
$[CoNO(CO)_3]$ (**93**) catalyzes the carbonylation of benzyl bromides and chlorides to give carboxylic acids.[403] The reactions, carried out in a two-phase system, occurred at normal temperature and pressure and their behaviour was quite different to that observed when $[Co_2(CO)_8]$ is used as catalyst. The anion $[CoH(NO)(CO)_2]^-$ is believed to be a key intermediate, formed by attack of hydroxide on (**93**) followed by loss of CO_2. Ketones, bibenzyls and other by-products were detected in low yields. The mechanism of the carbonylation is given in Scheme 24.

$Co(OAc)_2$ in the presence of sodium hydride and a sodium alkoxide has been used to catalyze the carbonylation of aryl bromides, giving mixtures of carboxylic acids and esters, again at normal pressure.[404] When amines were present, amides were formed. Unfortunately, nothing is known about the nature of the cobalt complexes involved.



Scheme 24

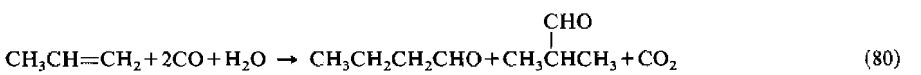
From the hydroesterification of 1-decene the cluster $[Co_3(H)_2py_5(CO)_9]$ has been isolated.[405] In the presence of 2-vinylpyridine, intermediates having the partial structure (**94**) were detected by NMR spectroscopy. This was believed to be an intermediate in the catalytic hydroesterification of 2-vinylpyridine to methyl 3-(2-pyridyl)propionate (equation 79).



(79)

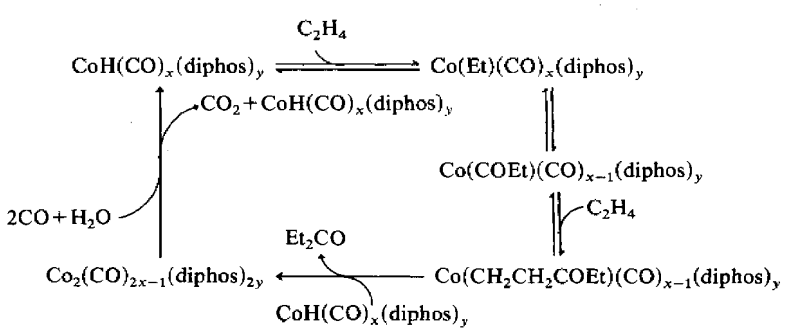
(**94**)

In presence of diphos, $[Co_2(CO)_8]$ catalyzes the reaction of propylene with CO and H_2O to give aldehydes (Reppe hydroformylation, equation 80).[406] The reaction requires high temperature



(80)

and pressure. Induction periods were observed and were attributed to formation of hydrido complexes of uncertain composition, $[CoH(CO)_x(diphos)_y]$, which lead to catalysis. In the presence of a large excess of propylene, di-*n*-propyl ketone became the major product. Under these conditions the ligands PBu_3, PPh_3, $P(OPh)_3$, $Ph_2PC{\equiv}CPPh_2$, $Ph_2As(CH_2)_2PPh_2$ and $Ph_2P(CH_2)_nPPh_2$ ($n = 1$–4) were all investigated. The best ligands for ketone formation were diphos and $Ph_2PC{\equiv}CPPh_2$.[407] Using $[Co_2(CO)_8]$ and diphos, ethylene gave diethyl ketone with a selectivity of 99%.[408] The suggested general reaction mechanism is given in Scheme 25.



Scheme 25

The small amount of propanal formed in the reaction (less than 1%) arises from the reaction of the hydride with the acyl. The same catalyst system converted methyl acrylate to dimethyl

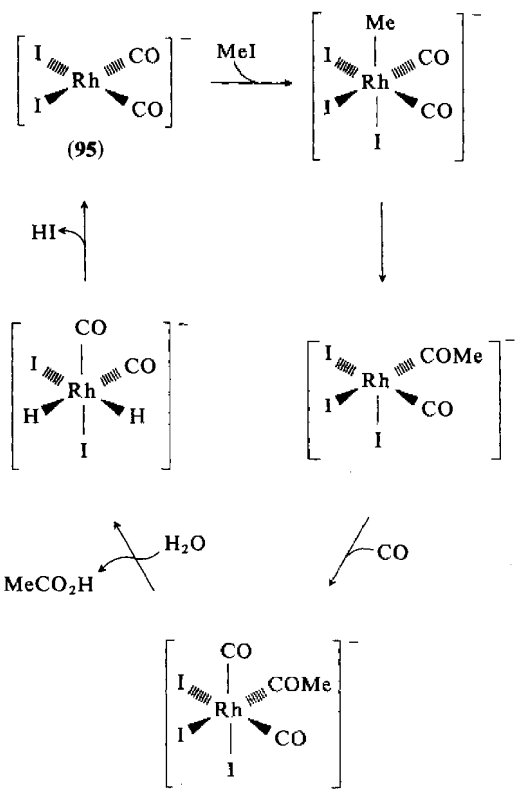
4-oxopimelate (equation 81) in a yield of 94%, and a mechanism analogous to Scheme 25 was proposed.[409]

$$CH_2{=}CHCO_2Me + 2CO + H_2O \xrightarrow[\text{diphos}]{[Co_2(CO)_8]} OC(CH_2CH_2CO_2Me)_2 \quad (81)$$

The synthesis of bifurandiones from acetylenes and CO using $[Co_2(CO)_8]$ in presence of PBu^n_3 or $P(OMe)_3$ has been briefly reported.[410]

61.2.5.4 Rhodium

As mentioned in the previous section, the carbonylation of methanol to acetic acid is an important industrial process. Whereas the $[Co_2(CO)_8]$-catalyzed, iodide-promoted reaction developed by BASF requires pressures of the order of 50 MPa, the Monsanto rhodium-catalyzed synthesis, which is also iodide promoted and which was discovered by Roth and co-workers, can be operated even at normal pressure, though somewhat higher pressures are used in the production units.[411–413] The rhodium-catalyzed process gives a methanol conversion to acetic acid of 99%, against 90% for the cobalt reaction. The mechanism of the Monsanto process has been studied by Forster.[414] The anionic complex *cis*-$[RhI_2(CO)_2]^-$ (**95**) initiates the catalytic cycle, which is shown in Scheme 26.

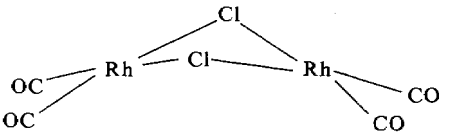


Scheme 26

Reaction (78) regenerates MeI from methanol and HI. Using a high-pressure IR cell at 0.6 MPa, complex (**95**) was found to be the main species present under catalytic conditions, and the oxidative addition of MeI was therefore assumed to be the rate determining step. The water-gas shift reaction (equation 70) also occurs during the process, causing a limited loss of carbon monoxide. A review of the cobalt-, rhodium- and iridium-catalyzed carbonylation of methanol to acetic acid is available.[415]

Kinetic studies of the acetic acid synthesis catalyzed by $RhCl_3{\cdot}3H_2O$ have confirmed that the oxidative addition of MeI is the rate determining step.[416–418] The effect of nitrogen and phosphorus ligands on the reaction has been studied, and bidentate ligands were shown to inhibit the reaction almost completely.[419] A kinetic study of the solvent dependence of the reaction showed that

solvents of medium polarity such as ketones led to both high selectivity and high activity when $RhCl_3 \cdot 3H_2O$ or $[Rh_2Cl_2(CO)_4]$ (**96**) was used as catalyst precursor.[420]



(**96**)

Ethanol[421] is carbonylated to propionic acid, and isopropanol[422] is carbonylated to *n*- and iso-butyric acids. In the latter case it is not known whether the isomerization occurs in the alcohol, the iodide or the rhodium–alkyl complex.

In presence of hydrogen, $RhCl_3$ and $[RhH(CO)(PPh_3)_3]$ (**34**) catalyze the homologation of methanol to ethanol, again with methyl iodide as promoter. The mechanism was believed to involve the oxidative addition of methyl iodide followed by CO insertion to give an acyl. This then either underwent direct hydrogenation to ethanol or gave acetaldehyde which was subsequently reduced. The sequence generates HI which reacts with methanol according to equation (78), regenerating methyl iodide.[423]

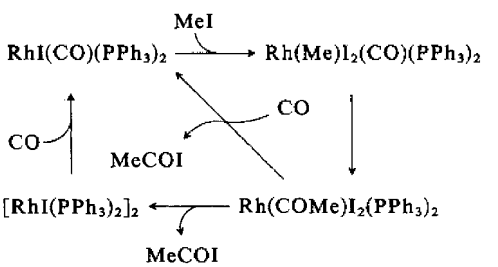
Dimethyl ether has been carbonylated in two steps to give acetic anhydride (equation 82). The first step is the faster of the two. The catalyst was $RhCl_3 \cdot 3H_2O$ in presence of PPh_3 and $[Cr(CO)_6]$. Nothing appears to be known about the mechanism.[424]

$$MeOMe + CO \rightarrow MeCOMe \xrightarrow{CO} MeCOCMe \quad (82)$$

$$MeCCH_2CH_2OR + CO \rightarrow MeCCH_2CH_2COR \quad (83)$$

Esters of levulinic acid have been synthesized by carbonylation of 4-alkoxy-2-butanones (equation 83). Methyl iodide was used as promoter and the best results were obtained with $[RhCl(PPh_3)_3]$ (**23**), $[RhI(CO)(PPh_3)_2]$ or $RhCl_3 \cdot 3H_2O$ and PBu^n_3 as catalyst precursors. Cleavage of the ether linkage with HI to give 4-iodo-2-butanone was proposed as the initial step in the reaction.[425] $[RhCl(CO)(PPh_3)_2]$ (**71**) has been shown to catalyze the carbonylation of epoxides to β-lactones, but uncertainty exists regarding the mechanistic details.[426] The homologation of acetic acid is catalyzed by complexes such as $[Rh(acac)_3]$, $RhCl_3$ and Rh_2O_3.[385] The main product is propionic acid but butyric and valeric acids were also formed.

The carbonylation of methyl acetate to acetic anhydride is likely to become an industrial process in the near future.[424,427] $RhCl_3 \cdot 3H_2O$ is typically used as catalyst precursor and an iodide promoter is used. A mechanistic study indicated that methyl iodide formed from the ester and HI is carbonylated as in acetic acid synthesis (Scheme 26). The resulting acyl, perhaps *via* reductive elimination of acetyl iodide, converts the acetic acid formed in the ester cleavage to acetic anhydride.[428–430] $[RhI(CO)(PPh_3)_2]$ also catalyzes the reaction though apparently more slowly than complex (**95**).[430,431] The mechanism of this reaction is given in Scheme 27.

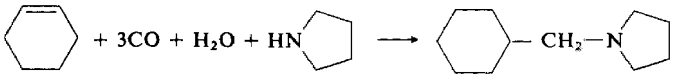


Scheme 27

The five-coordinate acyl complex may not be mononuclear. Using a rhodium complex in presence of a diamine, alkenes were converted to alcohols according to reaction (84).

$$RCH{=}CH_2 + 3CO + H_2O \rightarrow RCH_2CH_2CH_2OH \text{ or } \underset{\displaystyle CH_2OH}{\overset{\displaystyle |}{RCHCH_3}} + 2CO_2 \quad (84)$$

$[Rh_2Cl_2(CO)_4]$ (**96**), $[RhCl(PPh_3)_3]$ (**23**) and $RhCl_3 \cdot 3H_2O$ were all employed as catalysts though none was as good as $[Rh_6(CO)_{16}]$. The most suitable diamines were $Me_2N(CH_2)_nNMe_2$ ($n = 2, 3$) and 4-dimethylaminopyridine. The linear alcohols predominated.[432] If amines are present in reactions such as (**84**), aminomethylation takes place. This provides a ready synthesis of secondary and tertiary amines containing a $-CH_2+N\leq$ group. A typical example is given in equation (85).[433]

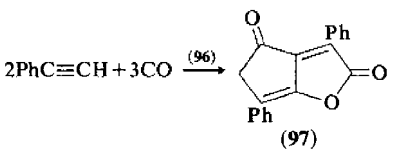


(85)

Although the reaction was first discovered more than 30 years ago, the mechanism is still not certain. An acyl complex was believed to be an intermediate. This then reacted with the amine to give an imine or enamine.[433] The complexes $[RhCl_3py_3]$, $[RhCl(NH_3)_5]^{2+}$ and $[Rh_6(CO)_{16}]$ all catalyzed the reaction with very similar conversion and selectivity, and in view of the high temperature and CO pressure it seems likely that similar carbonyl complexes are involved in all three cases.

$[RhCl(PPh_3)_3]$ (**23**) and $[RhCl(CO)(PPh_3)_2]$ (**71**) catalyze the formation of enol silyl ethers and derivatives according to equation (86). Both the (*E*) and (*Z*) isomers of the product are obtained.[435a] The dinuclear complex $[Rh_2Cl_2(CO)_4]$ (**96**) catalyzes the reaction of phenylacetylene with carbon monoxide to give 3,6-diphenyl-1-oxabicyclo-[3.3.0]-octa-3,6-diene-2,4-dione (**97**) (equation 87).[435b]

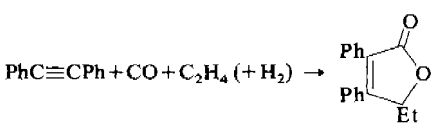
$$n\text{-}C_4H_9CH{=}CH_2 + CO + HSiEt_2Me \rightarrow n\text{-}C_5H_{11}CH{=}CHOSiEt_2Me \quad (86)$$



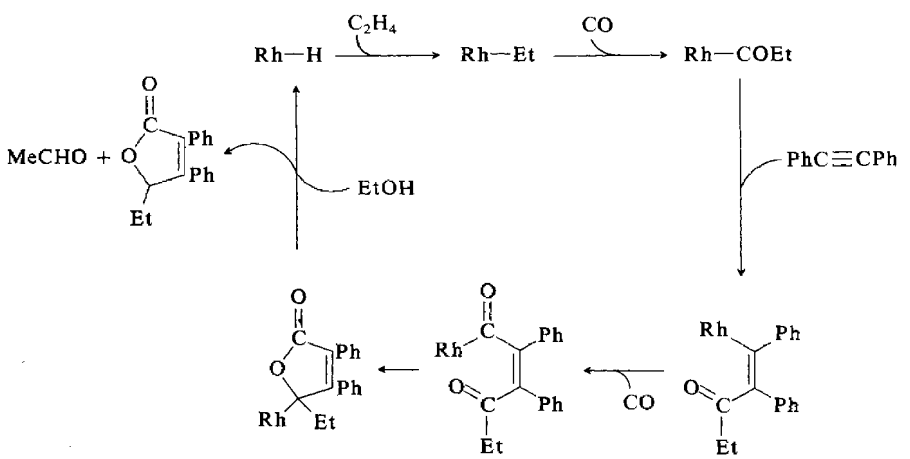
(87)

(**97**)

In presence of an alkene, furanone derivatives were obtained (equation 88).[436] The hydrogen needed for the reaction was derived from the solvent, ethanol. $[RhCl(CO)(PPh_3)_2]$ (**71**), $[RhCl(PPh_3)_3]$ (**23**) and $RhCl_3 \cdot 3H_2O$ as well as binary carbonyls could all be used as catalysts. The mechanism shown in Scheme 28 was proposed.



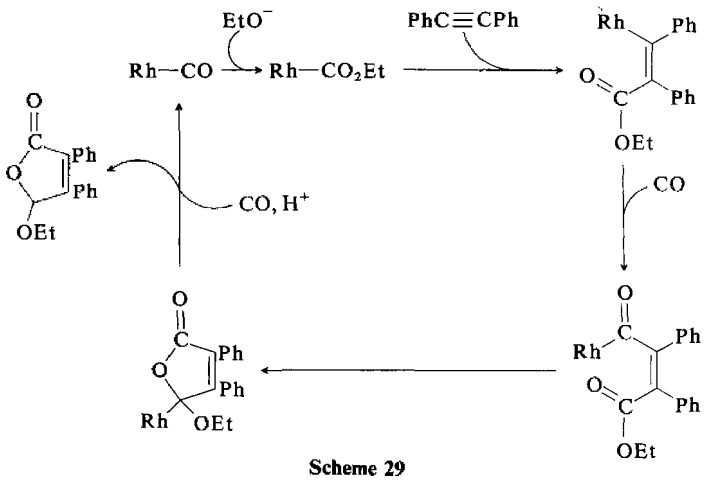
(88)



Scheme 28

In presence of a mild base such as Na_2CO_3 or NaOAc, a hydroesterification to furanones is possible (equation 89).[437] $RhCl_3 \cdot 3H_2O$ or a binary carbonyl was used as catalyst. Indanone derivatives were obtained as by-products. The mechanism probably involves the formation of an alkoxycarbonyl intermediate (Scheme 29).

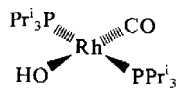
$$PhC{\equiv}CPh + 2CO + EtOH \rightarrow \text{(Ph, Ph, O, OEt)} \quad (89)$$



Scheme 29

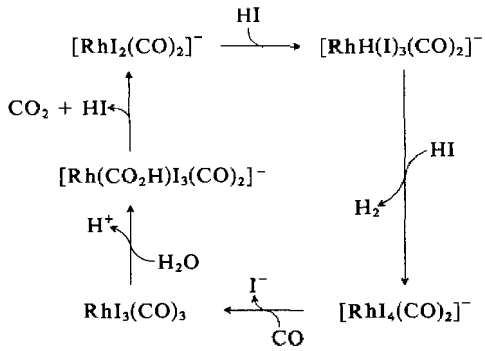
[Rh(acac)(CO)$_2$] in presence of 2-hydroxypyridine has been shown to catalyze the hydrogenation of CO at high temperature and pressure. The reaction is of poor selectivity, more than a dozen C_1, C_2 and C_3 products being formed.[438] Ethylene glycol was the major product and formaldehyde was believed to be a key intermediate. Although its formation from H_2 and CO is thermodynamically very unfavourable, it would only need to be present in low concentration.

Many rhodium complexes catalyze the water-gas shift reaction (equation 70). [RhCl(PPh$_3$)$_3$] (**23**), [RhCl(cod)]$_2$, [Rh(nbd)(diphos)]$^+$, [Rh(cod)diphos)]$^+$, [Rh(cod)(PMePh$_2$)$_2$]$^+$ and [Rh(cod)(mSPPh$_2$)$_2$]$^-$ (mSPPh$_2$ = **31**) all catalyzed the hydrogenation of benzalacetone using CO and H_2O as the hydrogen source.[439] A similar hydrogenation of methyl crotonate has been described, in which *trans*-[Rh(OH)(CO)(PPr$^i_3$)$_2$] (**98**) is the catalyst.[440] This complex was formed *in situ* from [Rh(H)$_2$(O$_2$COH)(PPr$^i_3$)$_2$] or from [RhCl(C$_7$H$_8$)]$_2$ and PPr$^i_3$ and Bu^{n}Li. In these reactions, hydroformylation also occurred.



(**98**)

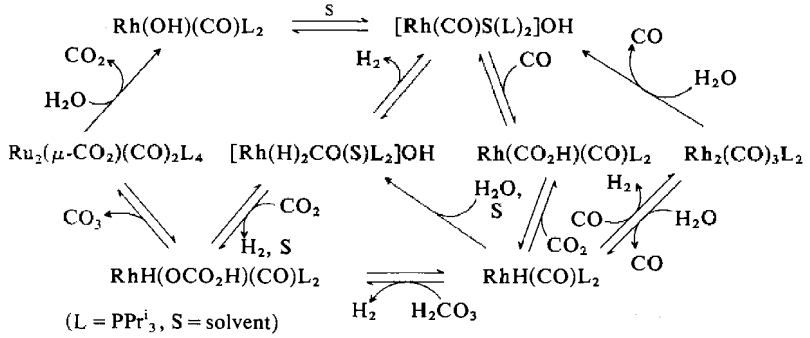
[Rh$_2$Cl$_2$(CO)$_4$] (**96**) in acidic solution also catalyzes the water-gas shift. In presence of excess iodide, [RhI$_2$(CO)$_2$]$^-$ (**95**) is believed to be the active rhodium species and the reaction required only mild conditions.[441,442] The proposed mechanism is given in Scheme 30.



Scheme 30

Other iodocarbonyl complexes might be present, depending on the CO pressure. In a further study of the water-gas shift reaction a large number of phosphine-containing rhodium complexes were investigated as catalysts. They were mainly either neutral or cationic carbonyl derivatives

and are too numerous to mention here.[443] The mechanism was studied using complex (**98**) as precursor, and differs from that with the phosphine-free complex (**95**) in that carbonate intermediates are involved. The chemistry is summarized in Scheme 31. As no kinetic study was undertaken, the relative importance of the different pathways is not known. The solvent (*S*) was typically acetone or pyridine.



Scheme 31

The complexes $[Rh(bipy)_3]^{3+}$, $[RhCl_2(bipy)_2]^+$ and $[Rh(OH_2)_2(bipy)_2]^{3+}$ also catalyze reaction (70), with the latter two being most effective. Using sulfonated bipyridyl or phenanthroline derivatives, water-soluble catalysts were prepared.[444]

If $[RhCl(CO)(PPh_3)_2]$ (**71**) is treated with an aryl azide such as *p*-tolyl azide in presence of CO, reactions (90) and (91) occur.

$$RhCl(CO)(PPh_3)_2 + MeC_6H_4N_3 \rightarrow RhCl(N)_2(PPh_3)_2 + MeC_6H_4NCO \quad (90)$$

$$RhCl(N)_2(PPh_3)_2 + CO \rightarrow RhCl(CO)(PPh_3)_2 + N_2 \quad (91)$$

The nitrogen complex has only transient existence. These reactions permit a catalytic carbonylation of azides to isocyanates at low CO pressure.[445] The complexes $[RhX(CO)L_2]$ (X = Cl, Br, F; L = $P(OPh)_3$, PPh_3, $P(4\text{-}ClC_6H_4)_3$, $P(4\text{-}MeOC_6H_4)_3$, $P(C_6H_{11})_3$, PBu^n_3) were investigated and $[RhCl(CO)(PBu^n_3)_2]$ gave the highest rate for the carbonylation of *p*-tolyl azide. In a separate study, complex (**71**) and $[Rh(diphos)_2]^+$ were shown to catalyze the same azide carbonylation and also to give ureas in presence of aniline derivatives (equation 92) and carbamates in presence of alcohols (equation 93).[446,447]

$$p\text{-}RC_6H_4N_3 + CO + p\text{-}R'C_6H_4NH_2 \rightarrow p\text{-}RC_6H_4NHCONHC_6H_4R'\text{-}p \quad (92)$$

$$p\text{-}RC_6H_4N_3 + CO + EtOH \rightarrow p\text{-}RC_6H_4NHCO_2Et \quad (93)$$

In a reaction related to azide carbonylation, aromatic nitroso compounds also give isocyanates (equation 94). $[Rh_2Cl_2(CO)_4]$ (**96**), [RhCl(CO)$_2$py], $[RhCl(CO)(PPh_3)_2]$ (**71**) and $[RhCl(CO)\{P(OPh)_3\}_2]$ all catalyzed the reaction. Deoxygenation of the nitrosobenzene derivative was the rate determining step.[448] Nitrosomethane can be similarly carbonylated.[449–451]

$$RNO + 2CO \rightarrow RNCO + CO_2 \quad (94)$$

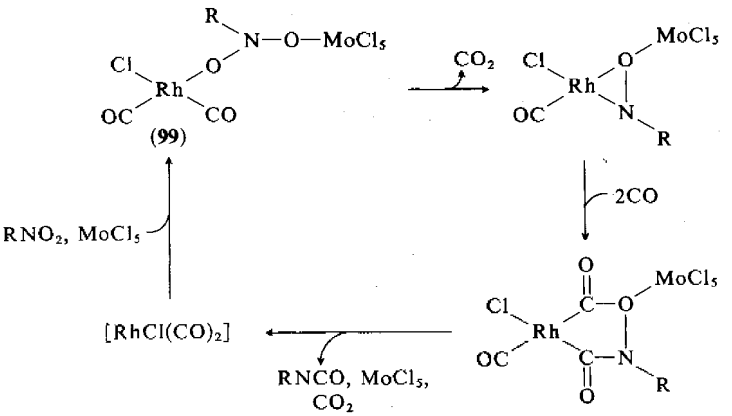
The more usual way of producing isocyanates by catalytic carbonylation employs the more readily available nitro compounds as starting materials (equation 95). There are a number of

$$PhNO_2 + 3CO \rightarrow PhNCO + 2CO_2 \quad (95)$$

reports on rhodium catalysts for this reaction. The complexes used include $RhCl_3 \cdot 3H_2O$ and $[Rh_2Cl_2(CO)_4]$ (**96**),[452] $[RhH(CO)(PPh_3)_3]$ (**34**)[453] and complex (**96**) in presence of pyridine[454] or in presence of a metal halide such as $MoCl_5$.[455–457] The mechanism proposed in the latter case is given in Scheme 32. $MoCl_5$ is believed to act as a Lewis acid which coordinates to one atom of the nitro group. Reaction of the resulting $RN(O)OMoCl_5$ entity with complex (**96**) leads to cleavage of the chloride bridges to give (**99**). The principal advantage of the presence of $MoCl_5$ is that it permits the reaction to be carried out at normal pressure, though raised temperature is still needed.[457]

A further reaction in which CO acts as a reducing agent is that with nitric oxide (equation 96).

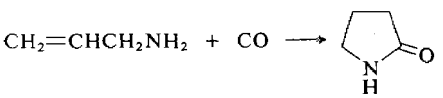
$$CO + 2NO \rightarrow CO_2 + N_2O \quad (96)$$



Scheme 32

It has become of increased importance because of environmental problems relating to oxides of nitrogen. With $RhCl_3 \cdot 3H_2O$ as catalyst the reaction proceeds slowly at normal temperature and pressure.[398] The anionic complex $[RhCl_2(CO)_2]^-$ has also been used as a catalyst and this leads to the formation of $[RhCl_2(CO)(NO)_2]^-$ (**100**) which is believed to take part in the catalytic cycle.[458] Complex (**100**) contains rhodium(III), as judged by the frequency of the CO stretching vibration and the nitrosyl ligands were regarded as coordinating as NO^-. At the end of the reaction, $[RhCl_2(CO)_2]^-$ was recovered quantitatively. The reaction requires aqueous acid. Two possible mechanisms were discussed, both of which involved complex (**100**).[459]

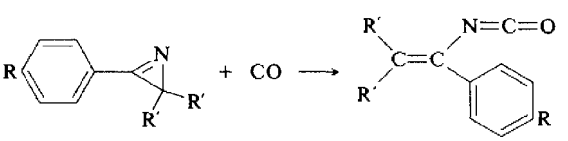
In a more recent study, $[Rh(NO)_2(PPh_3)_2]^+$ has been used as catalyst for reaction (96).[460] This system also shows an increased rate in presence of water, but this is far less marked than with complex (**100**). Dinuclear complexes form during the reaction but do not appear to be catalytically active. The details of the mechanism are not known at present.



(97)

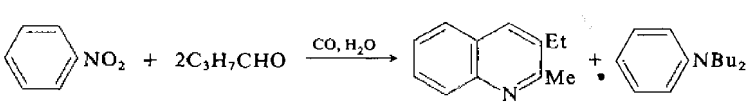
Some other rhodium-catalyzed reactions of CO are collected here. The cyclization of allyl amine to γ-butyrolactone (equation 97) is catalyzed by the complexes $RhCl_3$, $[Rh(acac)_3]$, $[Rh_2Cl_2(C_2H_4)_4]$, $[RhCl(PPh_3)_3]$ (**23**) and $[RhCl(CO)(PPh_3)_2]$ (**71**). If allyl chloride or iodide is used together with ammonia or a primary amine, analogous cyclizations occur.[461]

2-Arylazirines are carbonylated by $[Rh_2Cl_2(CO)_4]$ (**96**) to give isocyanates under mild conditions.[462] The reaction can be carried out at normal pressure and at room temperature or below. Vinyl isocyanates are produced (equation 98). By addition of alcohols or amines, carbamates or ureas were obtained.



(98)

In presence of $RhCl_3 \cdot 3H_2O$, $[Rh_2Cl_2(cod)_2]$, $[RhCl(PPh_3)_3]$ (**23**) or $[RhCl(CO)(PPh_3)_2]$ (**71**), alkylation of amines could be achieved using an aldehyde, CO and water.[463] $RhCl_3 \cdot 3H_2O$ effected the α-methylation of ketones in the presence of aqueous formaldehyde.[464] $RhCl_3 \cdot 3H_2O$ or $[RhCl(nbd)_2]$ catalyzes the formation of quinoline derivatives from aromatic nitrocompounds and aliphatic aldehydes again in presence of CO and water.[465] The aromatic compound is partly converted to the dialkylaniline derivative (equation 99). In all of these reactions the water-gas shift (equation 70) or a related reaction provides the reducing power.



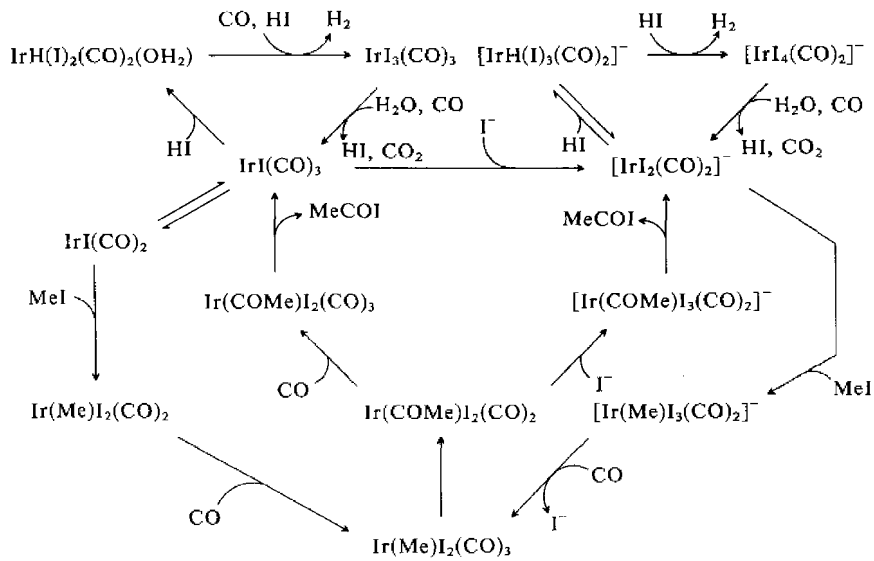
(99)

The carbonylation of cyclopropane catalyzed by $[Rh_2Cl_2(CO)_4]$ has been reported.[466] The selectivity of the reaction was poor, with up to eight products being formed. Cyclobutanone was the major carbonylation product.

A number of general reviews on carbonylation are available, which include rhodium-catalyzed reactions. They are listed at the end of Section 61.2.5.8.

61.2.5.5 Iridium

Iridium complexes in the presence of iodide promoters are, like rhodium complexes, efficient catalysts for the carbonylation of methanol to acetic acid.[416,467,468] Complexes of the type [IrCl(cod)L] (L = C_5H_5N, 3-ClC_5H_4N, 2-MeC_5H_4N) and $[Ir(cod)L']^+$ (L' = phen, bipy) have been used as precursors with various iodide promoters.[467] The cationic complexes gave the highest activities. It was shown that, under reaction conditions, anionic iodocarbonyl complexes of iridium were formed. $IrCl_4$ can be used as catalyst precursor and methyl iodide appears to be the best promoter.[416] The iridium-catalyzed carbonylation of methanol is mechanistically more complicated than that of rhodium.[468] The reaction can involve either neutral or anionic complexes of iridium depending on the reaction conditions, particularly on the acidity and the iodide concentration. The complexes $[IrI_2(CO)_2]^-$ and $[IrI_3(CO)_3]$ were isolated from the reaction mixture by addition of iodide and iodine respectively to it. This suggests that the complex $[IrI(CO)_3]$ is present in solution. The water-gas shift reaction (equation 70) can occur to a significant extent during iridium-catalyzed methanol carbonylation. The proposed mechanism is shown in Scheme 33.[468]



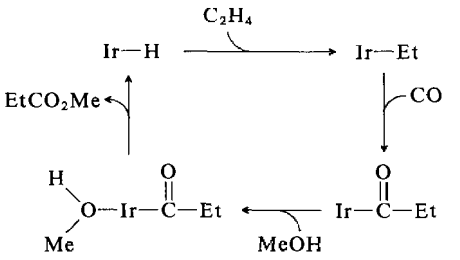
Scheme 33

The acetyl iodide formed reacts with water or methanol to give acetic acid or methyl acetate. The latter is subsequently hydrolyzed to acetic acid. Methyl iodide is regenerated according to equation (78). The synthesis of acetic acid from methanol catalyzed by complexes of cobalt, rhodium and iridium has been reviewed.[469]

Iridium complexes in the presence of iodide also catalyze the carbonylation of methyl acetate to acetic anhydride (equation 69). The reaction mechanism is similar to that of Scheme 33. The ester reacts with HI to give methyl iodide which is carbonylated as in Scheme 33 to acetyl iodide. This reacts with acetic acid to give the anhydride.[429,430]

If ethylene is present during the carbonylation of methanol catalyzed by $IrCl_4$, once again with MeI as promoter, methyl propionate is formed.[416] The reaction depends on the presence of iridium hydride species in solution, and a rhodium analogue of the reaction exists. The full details of the mechanism are not known but the basic steps are shown in Scheme 34. The intermediates are all believed to be complexes of iridium(III).

As mentioned above in connection with the acetic acid synthesis, iridium complexes catalyze the water-gas shift reaction (equation 70). From $IrCl_3 \cdot 3H_2O$ and sulfonated derivatives of bipy and phen, water-soluble catalysts were obtained.[444] Using dioxane as solvent, complexes of the type $[Ir(cod)L_2]^+$ (L = $PMePh_2$, PPh_3), $[Ir(cod)L']^+$ (L' = diphos, phen, 4,7-Me_2-phen, 4,7-Ph_2-phen, 3,4,7,8-Me_4-phen) and $[Ir(cod)X]^-$ (X = 4,7-diphenylphenanthroline disulfonate) also catalyzed the reaction, with the anionic species being most active.[470] The mechanism was thought



Scheme 34

to involve a hydroxycarbonyl intermediate which lost CO_2 to give a dihydride. Reductive elimination of hydrogen, coordination of CO and nucleophilic attack by water then close the cycle.

The complexes $[IrCl(CO)L_2]$ ($L = PPh_3$, $P(OPh)_3$ both catalyze the carbonylation of aryl nitroso compounds to give isocyanates (equation 94).[448]

61.2.5.6 Nickel

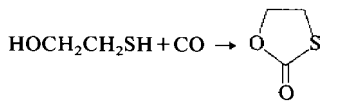
Many of the carbonylation reactions of nickel involve $[Ni(CO)_4]$ as catalyst. These are outside the scope of the present work and the companion volumes 'Comprehensive Organometallic Chemistry' should be consulted.

The carbonylation of dimethyl ether to methyl acetate (equation 68) is catalyzed by $[Ni(H_2O)_6]Cl_2$ in the presence of PPh_3 and $[Cr(CO)_6]$.[424] This reaction was much faster than the subsequent carbonylation of the ester to acetic anhydride. The nature of the complexes formed under reaction conditions is unknown. The reaction requires both high temperature and CO pressure.

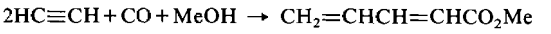
$[Ni(CO)_3py]$ catalyzes the carbonylation of 2-mercaptoethanol with ring closure (equation 100).[471] The product is *O,S*-ethylenethiocarbonate. A thiol complex, $[Ni(SCH_2CH_2OH)_2]$, was isolated from the reaction mixture and was also shown to catalyze the reaction, which occurred at a temperature and pressure only slightly above normal.

$[NiI(CO)_3]^-$ catalyzed the carbonylation of acetylene in the presence of methanol to give methyl 3-vinylacrylate (equation 101).[472] Unsaturated esters of higher molecular weight were also obtained.

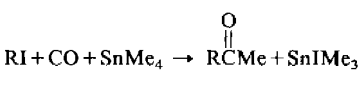
Methyl ketones can be prepared by the carbonylation of aryl, benzyl and thienyl bromides and iodides in the presence of tetramethyltin (equation 102). This reaction also requires raised temperature and pressure. $[Ni(CO)_2(PPh_3)_2]$ (**101**) was used as catalyst.[473]



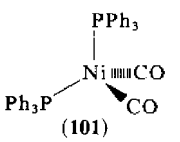
(100)



(101)

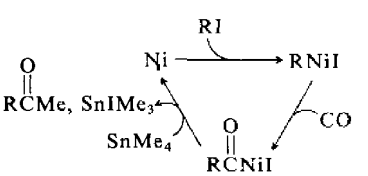


(102)



(**101**)

The complexes $[Ni(CO)_3PPh_3]$ and $[NiCl_2(PPh_3)_2]$ were less active, and $[NiCl_2(diphos)]$ gave only traces of product. The basic steps of the mechanism are given in Scheme 35.



Scheme 35

61.2.5.7 Palladium

Under oxidizing conditions, generally achieved by admission of oxygen itself, alcohols can be carbonylated to give oxalate or carbonate esters in the presence of palladium catalysts (equation 103).

$$ROH + CO \rightarrow RO_2CCO_2R + ROCO_2R \quad (103)$$

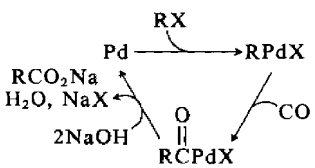
$PdCl_2$ in the presence of another metal chloride as co-catalyst and oxygen gave diethyl oxalate and diethyl carbonate from ethanol and CO.[474] The reaction requires both high temperature and pressure. $CuCl_2$ as co-catalyst gave the best yields of the oxalate ester. The details of the mechanism are not yet clear, but it is thought that attack of alcohol on coordinated CO gives an alkoxycarbonyl complex, which coordinates a second CO molecule *cis* to this group. Further nucleophilic attack of the alcohol on this second CO ligand could then promote formation of the oxalate ester. Phenol has been carbonylated to diphenyl carbonate in a two-phase system in presence of oxygen and NaOH as base (equation 104). A quaternary ammonium or phosphonium salt was used as a phase-transfer catalyst, and $[Mn(acac)_2]$ as co-catalyst. $PdBr_2$ was the palladium source and diphenyl carbonate was the only carbonylation product.[475]

$$2PhOH + CO \rightarrow (PhO)_2CO \quad (104)$$

The phase-transfer method has also been used for the synthesis of aryl, benzyl, vinyl and heterocyclic carboxylic acids by carbonylation of the corresponding halides (equation 105).[476]

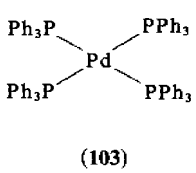
$$RX + CO + 2NaOH \rightarrow RCO_2Na + H_2O + NaX \quad (105)$$

The second mole of base is needed to effect reaction (10) and complete the catalytic cycle. $[PdCl_2(PPh_3)_2]$ (**102**) was used as catalyst in the presence of excess PPh_3. The basic steps of the mechanism are given in Scheme 36.

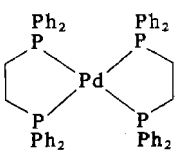


Scheme 36

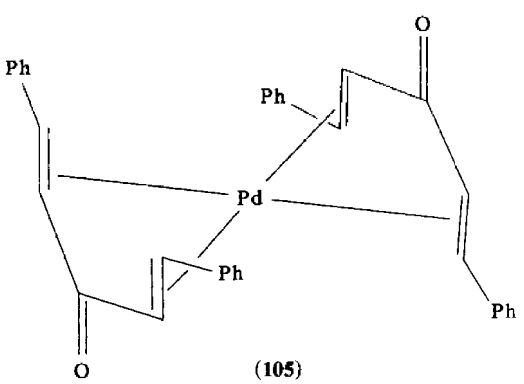
The phase-transfer method has also been employed for the carbonylation of benzylic halides to carboxylic acids.[477] The palladium(0) complexes $[Pd(PPh_3)_4]$ (**103**), $[Pd(diphos)_2]$ (**104**) and $[Pd(DBA)_2]$ (**105**; DBA = dibenzylideneacetone) were used as catalysts. With (**103**) and (**104**) the carboxylic acid was the major product. Complex (**105**) gave little or none of the acid, the toluene and bibenzyl derivatives corresponding to the benzyl halide used being formed. Benzyl esters of the carboxylic acid were sometimes present as minor products. The reaction has been adapted to provide a new synthesis of anthranilic acid derivatives (equation 106).[478] Tri-*n*-butylamine was used to neutralize the HBr formed.



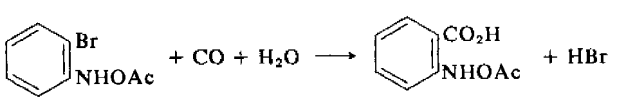
(**103**)



(**104**)



(**105**)

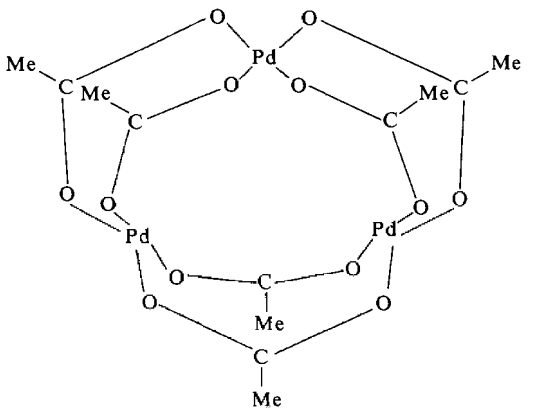


(106)

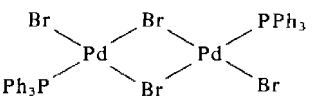
Heck and co-workers have reported the catalytic carbonylation of aryl and vinyl bromides and iodides and of benzyl chlorides in the presence of alcohols to give esters.[479] The general reaction is summarized in equation (107) in which RX represents the above organic halides.

$$RX + CO + R'OH + R''_3N \rightarrow RCOOR' + R''_3NH^+ X^- \quad (107)$$

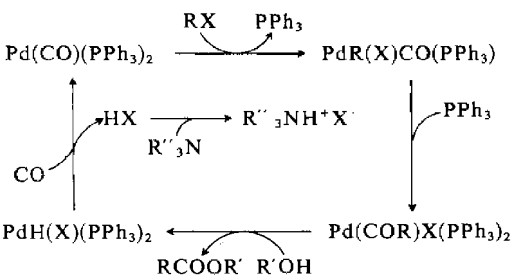
The reactions occur at normal pressure of CO but require raised temperatures. The complexes employed as catalyst precursors were $[Pd(OAc)_2]$ (**106**), $[PdI(Ph)(PPh_3)_2]$ (**107**), $[PdBr(Ph)(PPh_3)_2]$ (**108**), $[Pd_2Br_4(PPh_3)_2]$ (**109**), $[PdBr_2(PPh_3)_2]$ (**110**) and complex (**102**). Organic iodides reacted with (**106**) alone, otherwise the presence of PPh_3 was necessary. Electron withdrawing substituents in the aryl halides accelerated the reaction and electron releasing substituents hindered it. The palladium(II) complexes are reduced under the reaction conditions by alcohol and CO to give the palladium(0) species $[Pd(CO)(PPh_3)_2]$. This undergoes oxidative addition of the organic halide to initiate the catalytic cycle. The proposed mechanism is given in Scheme 37.



(**106**)

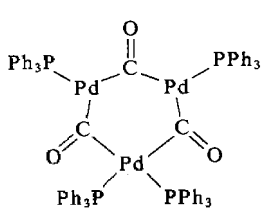


(**109**)

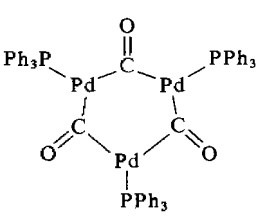


Scheme 37

The product of the oxidative addition may be $[PdX(R)(PPh_3)_2]$ and not the carbonyl complex shown. Inorganic bases such as NaOAc can also be used in these reactions.[480] Complex (**102**) was used here as catalyst precursor. In a further study of the reaction the complexes $[Pd(CO)(PPh_3)_3]$ (**111**), $[Pd_3(CO)_3(PPh_3)_4]$ (**112**), $[Pd_3(CO)_3(PPh_3)_3]$ (**113**) and complex (**102**) were used as catalysts with diethylamine as base.[481] The presence of an acyl intermediate was confirmed. Some of these reactions could be carried out at normal temperature and pressure.



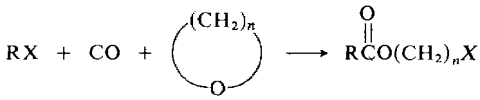
(**112**)



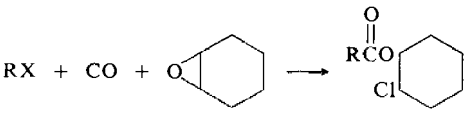
(**113**)

With complex (**102**) as catalyst, reaction (107) has been used to prepare a precursor of the natural product curvularin.[482] If cyclic ethers are used instead of alcohols, ω-haloesters are

obtained (equation 108).[483] Epoxides can be used in a similar manner (equation 109). Complex (**107**) was used as catalyst. No base is needed in this variant of the reaction.

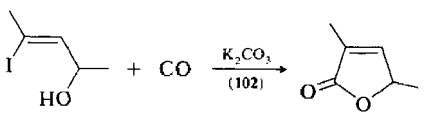


(108)



(109)

If the halide and the hydroxy group are present in the same molecule, reaction (107) leads to the synthesis of lactones.[484] With complex (**102**) as catalyst a series of butenolides were prepared in good yields from vinyl iodides (equation 110). Four- and six-membered ring lactones and α-methylene lactones were prepared.[485,486] The mechanism proposed was analogous to that of Scheme 37. This cyclization has been used in the synthesis of the natural product zearalenone.[487] $PdCl_2$ was the catalyst.



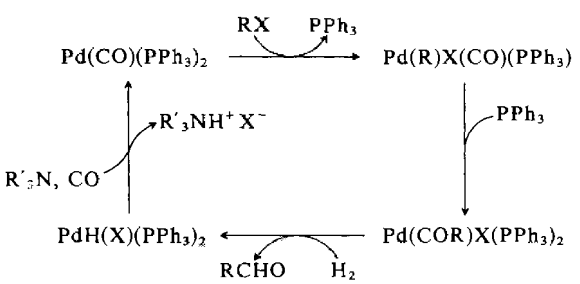
(110)

Aryl, vinyl and heterocyclic bromides and iodides in the presence of H_2, CO and a base react to give aldehydes (equation 111). $[PdI_2(PPh_3)_2]$ (**114**) or its analogues (**102**) and (**110**) were used as catalysts. The reaction requires both high temperature and pressure.[488] In some cases, aroyl chlorides are also converted to aldehydes under these conditions.

$$RX + H_2 + CO + R'_3N \rightarrow RCHO + R'_3NH^+X^- \quad (111)$$

Reaction of the catalyst precursor $[PdX_2(PPh_3)_2]$ (X = halide) with H_2, CO and two moles of base is believed to give $[Pd(CO)(PPh_3)_3]$ (equation 112). This then undergoes oxidative addition and dissociation of a PPh_3 ligand. The proposed mechanism is given in Scheme 38.

$$PdX_2(PPh_3)_2 + H_2 + CO + 2R'_3N \xrightarrow{PPh_3} Pd(CO)(PPh_3)_3 + 2R'_3NH^+X^- \quad (112)$$



Scheme 38

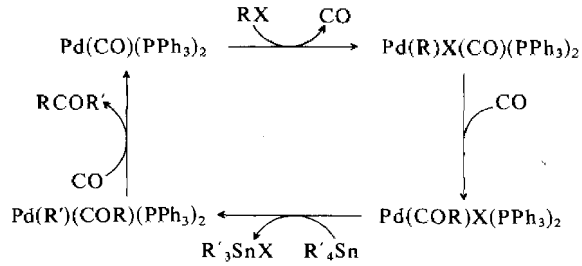
As with other palladium-catalyzed reactions of organic halides, if the group R is such as to permit a β-hydride elimination, reaction (7) may occur preferentially.

Unsymmetrical ketones can be obtained by the palladium-catalyzed carbonylation of aryl, alkyl and vinyl bromides and iodides in the presence of tetraalkyl- or tetraaryl-tin compounds (equation 113).[489,490] The catalyst precursors used were complexes (**102**), (**107**) and $[PdCl_2(AsPh_3)_2]$.

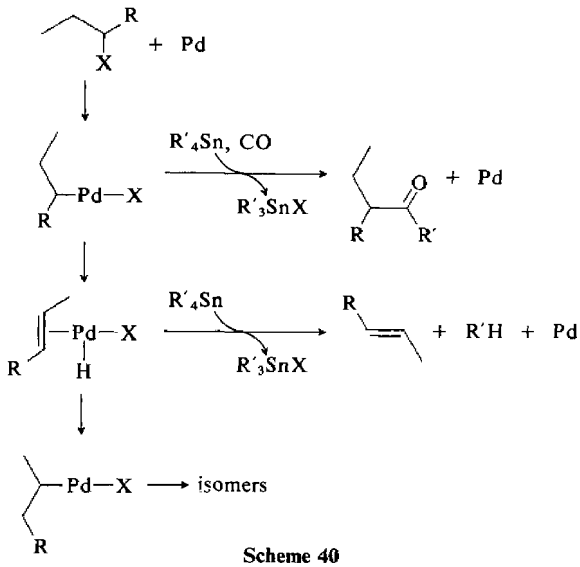
$$RX + CO + R'_4Sn \rightarrow \underset{\|}{\overset{O}{}}RCR' + R'_3SnX \quad (113)$$

When alkyl halides were used, some elimination occurred to give the corresponding alkene.[490] $[Pd(CO)(PPh_3)_2]$ was again believed to be formed *in situ* when PPh_3 complexes were used as catalysts. The mechanism of ketone formation is shown in Scheme 39.

For those cases where R is an alkyl group, the extended reaction sequence shown in Scheme 40 was invoked to explain the production of the alkene and the occurrence of isomerization.[490] $AsPh_3$ as ligand was found to favour the carbonylation reaction relative to PPh_3.



Scheme 39



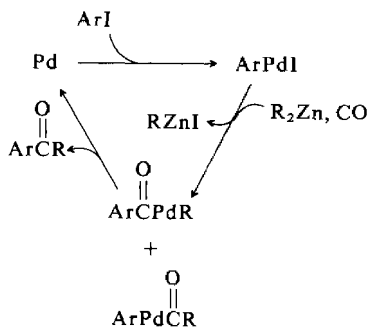
Scheme 40

At raised temperature and CO pressure, terminal acetylenes can replace the organotin derivatives, giving acetylenic ketones (equation 114).[491] Some of these reactions occur at normal pressure. Aryl, heterocyclic and vinyl bromides and iodides could be used. These reactions again required a stoichiometric quantity of base. The complexes (**102**), $[PdCl_2L_2]$ (L = 1,1'-bis(diphenylphosphino)ferrocene) and $[PdI(Ph)(AsPh_3)_2]$ were used as catalysts. The mechanism was not discussed.

$$RX + CO + HC{\equiv}CR' + R''_3N \rightarrow \underset{\displaystyle O}{\overset{\displaystyle \|}{R}}CC{\equiv}CR' + R''_3NH^+ X^- \qquad (114)$$

The reaction of an aryl and an alkyl iodide in presence of complex (**103**) and the Zn-Cu couple leads to alkyl aryl ketones in good yields (equation 115).[492] By-products such as ArR, ArH and Ar_2 were found in some cases. Replacement of alkyl iodides by benzyl chlorides gave benzyl ketones, but the formation of by-products due to coupling reactions was significant. Dialkylzinc complexes were formed here and the proposed mechanism is given in Scheme 41.

$$ArX + CO + RX \xrightarrow{Zn\text{-}Cu} \underset{\displaystyle O}{\overset{\displaystyle \|}{Ar}}CR \qquad (115)$$

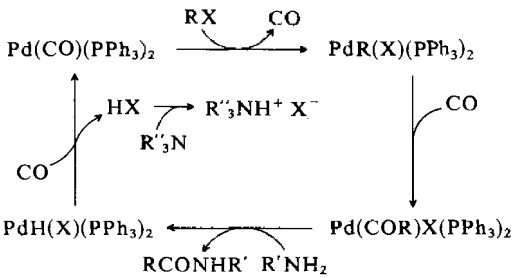


Scheme 41

The introduction of a primary or secondary amine into reaction (107) in place of the alcohol leads to the production of amides (equation 116).[493] The complexes used as catalyst precursors were (**102**), (**110**), (**114**) and (**108**). Complex (**110**) was most often used.

$$RX+CO+R'NH_2+R''_3N \rightarrow RCONHR'+R''_3NH^+X^- \quad (116)$$

The reaction can be carried out with aryl, heterocyclic and vinyl bromides and iodides and with some vinyl chlorides. It requires raised temperature but only normal CO pressure. If the primary or secondary amine is a strong enough base, it can be used in excess and the tertiary amine is not needed. The mechanism given in Scheme 42 was proposed for the reaction. It was not known whether the primary amine enters the reaction sequence at the point shown or at an earlier stage.



Scheme 42

The initial reduction of the palladium(II) precursors to $[Pd(CO)(PPh_3)_2]$ occurs according to equation (117).

$$PdX_2(PPh_3)_2+2CO+R'NH_2 \rightarrow Pd(CO)(PPh_3)_2+(R'NH)_2CO+2HX \quad (117)$$

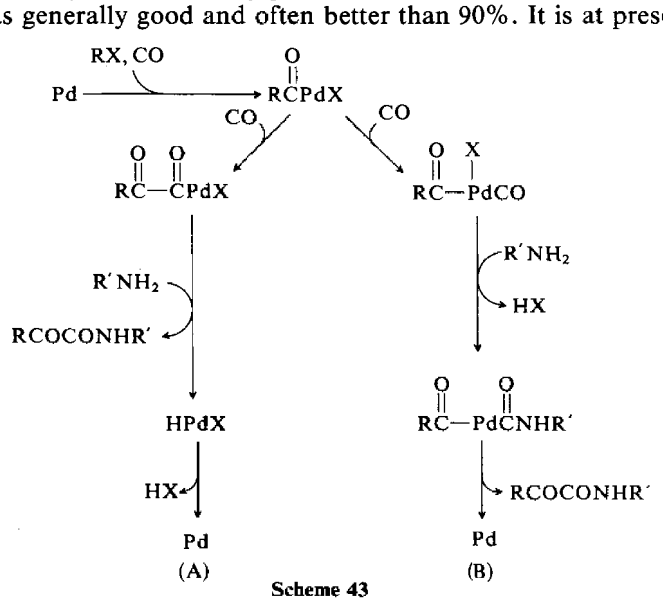
Using $[PdI(Ph)(PPh_3)_2]$ (**107**) as catalyst, it has been shown that at higher temperature and CO pressure amides may be formed directly from tertiary amines according to equation (118).[494] This reaction appears to be limited to R' = Et if reasonable yields are to be attained.

$$RX+CO+R'_3N \rightarrow RCONR'_2+R'X \quad (118)$$

In a further variant of this type of carbonylation, aryl, vinyl and heterocyclic bromides and iodides underwent a double carbonylation to give α-ketoamides (equation 119).

$$RX+2CO+2R'_2NH \rightarrow RCOCONR'_2+R'_2NH_2^+X^- \quad (119)$$

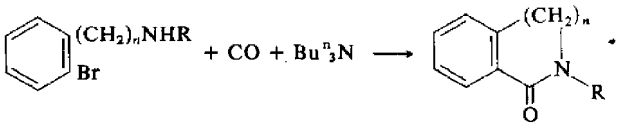
This reaction appears to be limited to secondary amines, which were used in excess.[495,496] Simple amides were usually obtained as by-products in these reactions, though the selectivity to the α-ketoamides was generally good and often better than 90%. It is at present not completely



Scheme 43

clear which reaction parameters affect the course of the reaction as regards the occurrence of single or double carbonylation, but it is clear that alkyl- or dialkyl-phosphines favour the latter course. Many complexes have been used as catalyst precursors for the reaction. The best complexes for double carbonylation were $PdCl_2$, $[PdCl_2(NCPh)_2]$, $[PdCl_2(PMePh_2)_2]$, $[PdCl_2(PMe_2Ph)_2]$, $[PdBr(Ph)(PMePh_2)_2]$, $[PdCl_2(PEtPh_2)_2]$, $[PdCl_2(PEt_2Ph)_2]$, $[PdCl_2(DIOP)]$, $[PdCl_2\{Ph_2P(CH_2)_4PPh_2\}]$ and $[PdI(Ph)(PPh_3)_2]$ (**107**). The precise mechanism is uncertain. An acyl complex is believed to be formed by the oxidative addition of the organic halide to palladium(0) followed by insertion of CO. There are then two possibilities for the production of α-ketoamides and they are given in Scheme 43.

The above synthesis of simple amides has been adapted to intramolecular reactions leading to lactams.[497] Five-, six- and seven-membered ring benzolactams were prepared (equation 120).



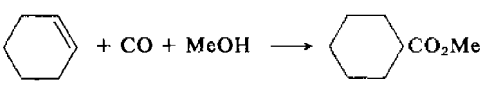
(120)

$[Pd(OAc)_2]$ in the presence of PPh_3 was used as catalyst. The use of vinyl bromides in lactam formation has also been reported.[498] Imides were obtained from aryl bromides. The method has further been applied to the synthesis of diazepam and 1,4-benzodiazepines[499] and to α-methylene lactams and lactones.[500,501] In connection with the synthesis of natural products, the reaction has been employed in the preparation of hexadehydrohimbane,[502] anthramycin[503] and berbine derivatives.[504] The catalyst was prepared *in situ* from $[Pd(OAc)_2]$ (**106**) and PPh_3 in all cases. The mechanism of lactam formation is analogous to that for amides (Scheme 42).

A brief review on the palladium-catalyzed carbonylation of organic halides has appeared.[505]

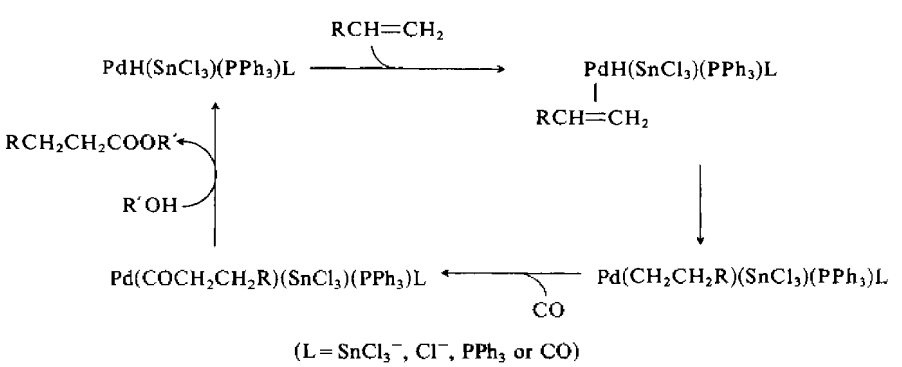
$PdCl_2$ in presence of PPh_3 catalyzes the hydrocarboxylation of alkenes at raised temperature and CO pressure (equation 121).[506] Both the normal and branched isomers of the acid are formed. The normal isomer is generally the major product if R is an alkyl group. Various other phosphorus ligands were tried and tri-*o*-tolylphosphine gave the highest ratio of linear to branched acids. Use of an alcohol in place of water in equation (121) leads to the formation of esters (hydroesterification). Thus cyclohexene and methanol gave methyl cyclohexanecarboxylate in high yield using $PdCl_2$ and PPh_3 as catalyst precursor. This reaction does not have the problem of isomer formation (equation 122).[507]

$$RCH{=}CH_2 + CO + H_2O \rightarrow RCH_2CH_2CO_2H + RCH(Me)CO_2H \quad (121)$$



(122)

In a study of the hydroesterification of 1-heptene the complexes $[PdCl_2L_2]$ ($L = PPh_3$, $AsPh_3$, $P(OPh)_3$, PMe_2Ph, $P(1\text{-}MeOC_6H_4)_3$, $P(4\text{-}ClC_6H_4)_3$, $P(4\text{-}MeOC_6H_4)_3$ or $P(o\text{-}tol)_3$) in the presence of Lewis acids such as $SnCl_2$, SnI_2, $GeCl_2$ and $PbCl_2$ were used as catalyst.[508] The combination $[PdCl_2\{P(p\text{-}tol)_3\}_2]$ plus $10SnCl_2$ gave the best yield and selectivity to the linear ester. Terminal alkenes generally reacted well, as did cyclooctene, but internal linear alkenes gave poor results. Primary alcohols performed far better than secondary ones. The catalyst precursor in the case of PPh_3 and $SnCl_2$ above is believed to give rise to a hydrido complex of the type $[PdH(SnCl_3)(PPh_3)L]$ ($L = SnCl_3^-$, PPh_3, CO or Cl). The expected reaction mechanism is given in Scheme 44.



Scheme 44

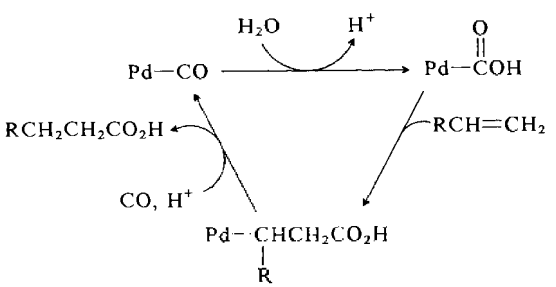
Isomer formation can occur at the alkene insertion step. This is probably reversible and the rates of the CO insertion for the alkyl complexes formed will therefore also affect the ultimate product distribution. Higher temperatures favour the formation of the branched isomer.[509] Often, the alcohol is used as solvent for these reactions. The addition of another solvent of lesser polarity has been shown to reverse the usual selectivity, giving the branched product as the major isomer. Again, complex (**102**) was used as catalyst.[510]

In the hydroesterification of styrene (equation 123) the isomer distribution was found to be very dependent on the phosphorus ligand used.

$$PhCH{=}CH_2 + CO + ROH \rightarrow PhCH_2CH_2CO_2R + \underset{\displaystyle CO_2R}{\overset{\displaystyle |}{PhCHMe}} \qquad (123)$$

Complex (**102**) gave only the branched isomer, whereas [$PdCl_2$(DIOP)] favoured the linear product. The same was found with α-methylstyrene, this time with almost complete regioselectivity in both cases.[511] The effect of chelate ring size on the selectivity was studied using the diphosphines $Ph_2P(CH_2)_nPPh_2$ ($n = 1$–6, 10). Complex (**102**) was included for comparison.[512,513] The six-, seven- and eight-membered chelate rings ($n = 3, 4, 5$) favoured the linear isomer slightly, the seven-membered ring giving the best result. For $n = 1, 6$ or 10 the branched isomer predominated, to a large extent in the latter two cases. This was also the case with the monodentate ligands PPh_3, PPh_2Bu, $PPh_2(CH_2Ph)$, PCy_3 and PBu_3, which gave almost complete specificity to the branched product. The effect was attributed to the stability of the chelate rings. Bisphosphine complexes favour the formation of the linear isomer on steric grounds, whereas in monophosphine species the branched alkyl complex is preferred. The larger, less stable chelate rings therefore show an increasing tendency to give rise to monophosphine complexes through chelate ring opening, favouring the branched product.[513] Interestingly, no catalytic reaction occurred when diphos was used as ligand. This would form the most stable, five-membered ring.

The hydroesterification of allyl acetate[461] and *N*-vinylphthalimide[514] has been studied using complex (**102**) in presence of excess PPh_3 or $SnCl_2$. Significant dependence of the regioselectivity of the solvent was again observed. 3,3,3-Trifluoropropene and pentafluorostyrene were subjected to hydroesterification and hydrocarbonylation using complex (**102**) or the complexes [$PdCl_2$L] (L = 1,1′-bis(diphenylphosphino)ferrocene, 1,4-bis(diphenylphosphino)butane) as catalysts.[515] By suitable choice of ligand and reaction conditions, either isomer of the respective products could be obtained in good yield. The selectivity changed markedly on changing the nucleophile from water to alcohol. This may be due to a change in the mechanism of the reaction to the alkoxycarbonyl route shown in Scheme 45, instead of the acyl route (Scheme 44).



Scheme 45

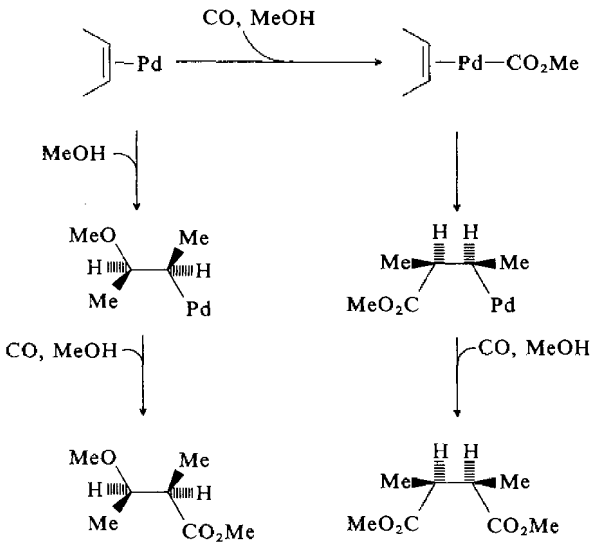
When the cluster $[Pd_4(CO)_4(O_2CMe)_4]\cdot 2MeCO_2H$ was dissolved in styrene and treated with methanol under an atmosphere of carbon monoxide, methyl cinnamate was formed.[516] This reaction was also believed to occur by an alkoxycarbonyl route. The reaction became catalytic when [$Pd(OAc)_2$] (**106**) was used in presence of NaOAc and a stoichiometric amount of copper(II) as reoxidant for the palladium(0) formed. Stille and co-workers have investigated this reaction, sometimes called carboalkoxylation, in detail. A basic difference between this reaction and the hydroesterification described above is that the oxidative nature of carboalkoxylation permits double functionalization of a double bond. Thus (*E*)- and (*Z*)-2-butene react readily with CO and methanol in the presence of a catalytic amount of $PdCl_2$ and a stoichiometric amount of $CuCl_2$ to give methyl 3-methoxy-2-methylbutanoate (equation 124).[517,518]

$$MeCH{=}CHMe + CO + MeOH \rightarrow MeCH(OMe)CH(CO_2Me)Me \qquad (124)$$

The addition to the double bond was, at least in the early stages of the reaction, exclusively *trans*. In presence of NaOAc this changed completely to give *cis* addition and the product under these conditions was dimethyl 2,3-dimethylsuccinate (equation 125).

$$MeCH{=}CHMe + CO \xrightarrow[NaOAc]{MeOH} MeCH(CO_2Me)CH(CO_2Me)Me \qquad (125)$$

The former reaction involves attack of methanol on the double bond as the first step. In presence of NaOAc however, carbomethoxylation occurs (Scheme 46).



Scheme 46

A number of linear and cyclic alkenes have been studied in this reaction. The presence of a base favoured the formation of diesters from linear alkenes, whereas cyclic alkenes gave diesters even in absence of base.[519] In a further study using dienes and unsaturated alcohols, ketones and esters, the dicarboxylation reaction could quite generally be achieved in good yields.[520,521]

In presence of CCl_4 and a base, alkenes react with CO and alcohols with $[Pd(OAc)_2]$ (**106**) and PPh_3 as catalyst precursor to give trichloromethyl derivatives (equation 126).[522] The ester was generally the major product. This reaction requires higher pressure than the above carboalkoxylations. Diphos and P(*o*-tol)$_3$ were as effective as PPh_3 as ligands but $P(OPh)_3$ and PBu_3 gave inferior results. The mechanism of the reaction is at present unknown.

$$RCH{=}CH_2 + CCl_4 + CO \xrightarrow{EtOH} \underset{CO_2Et}{\overset{R}{\diagup}\!\!\diagdown\!\!\overset{CCl_3}{}} + \underset{Cl}{\overset{R}{\diagup}\!\!\diagdown\!\!\overset{CCl_3}{}} \qquad (126)$$

Using (*E*)-alkenylpentafluorosilicates, unsaturated esters can be readily obtained by reaction with CO and methanol (equation 127).[523] $PdCl_2$ or $PdBr_2$ was generally effective as catalyst. Complex (**106**) was less satisfactory and no carbonylation occurred with $[PdCl_2(PPh_3)_2]$ (**102**).

$$K_2\left[\begin{array}{c} R \quad R' \\ \diagdown \quad / \\ C{=}C \\ / \quad \diagdown \\ H \quad SiF_5 \end{array}\right] + CO + MeOH \rightarrow \begin{array}{c} R \quad R' \\ \diagdown \quad / \\ C{=}C \\ / \quad \diagdown \\ H \quad CO_2Me \end{array} \qquad (127)$$

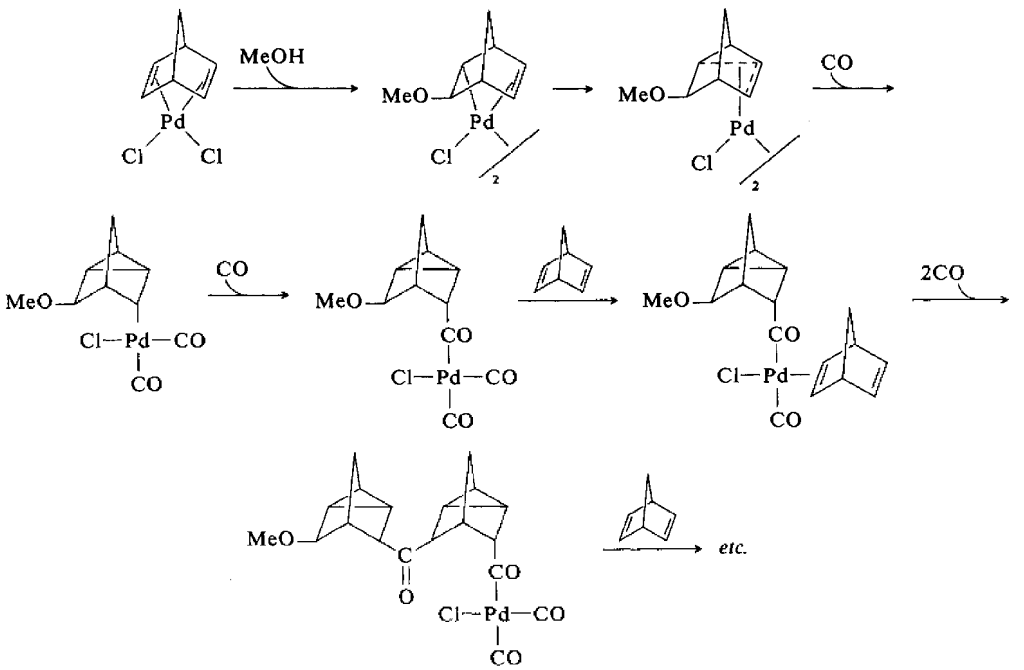
The hydroesterification of dienes gave both the unsaturated monoesters and saturated diesters.[524] In some cases, γ-ketoesters were obtained and carbonylation of 1,5-cyclooctadiene in absence of alcohol gave a ketone.[525] $[PdI_2(PBu_3)_2]$ was used as catalyst. If the catalyst contained a halide anion, butadiene underwent normal hydroesterification. When halide-free catalysts were used, the reaction took a different course. Dimerization of the diene occurred to give the ester of 3,8-nonadienoic acid as the major product (equation 128).[526–528]

$$2CH_2{=}CHCH{=}CH_2 + CO + ROH \rightarrow CH_2{=}CH(CH_2)_3CH{=}CHCH_2CO_2R \qquad (128)$$

Both $[Pd(OAc)_2]$ and $[Pd(acac)_2]$ were used as catalyst precursors, in the presence of PPh_3 or PBu^n_3. No catalysis occurred here in absence of the phosphorus ligand. When isoprene was carbonylated using $[Pd(OAc)_2]$ and PPh_3 as catalyst precursor, dimerization of the alkene did not take place, the ester of 4-methyl-3-pentenoic acid being formed as the only product.[529]

Because of its potential application to the synthesis of esters for lubricating oils, the dimerization–carbonylation of butadiene has received special attention. Basic phosphines such as PBu^n_3 and weakly basic tertiary amine solvents (quinoline, *N,N*-diethylaniline) were found to improve both the stability and activity of the catalyst system.[530] In a further report in which PPr^i_3 was used as phosphorus ligand it was found that the addition of maleic anhydride caused a marked increase in the catalytic activity. It was believed that through coordination it stabilized the palladium(0) complexes formed against precipitation as metal.[531]

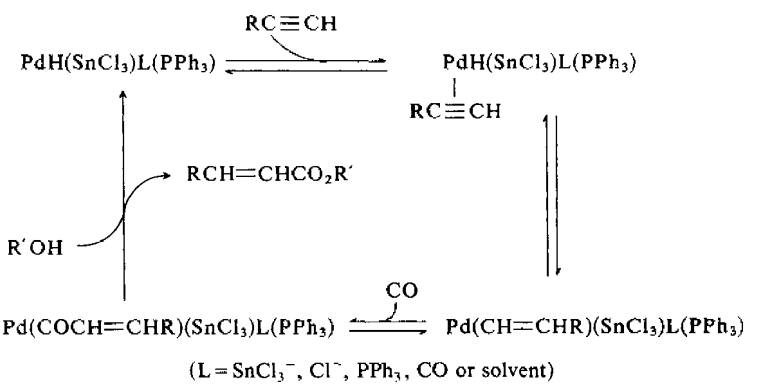
The carbonylation of norbornadiene in benzene solution catalyzed by $PdCl_2$ leads to the formation of a polymeric ketone.[532] This unusual reaction is believed to have the complex $[PdCl_2(nbd)]$ as its catalyst precursor, and the mechanism proposed for it is given in Scheme 47.



Scheme 47

A number of reports have appeared on the carbonylation of alkynes in presence of alcohols. Using the synthesis of methyl *trans*-2-octenoate from 1-heptyne (equation 129) as type reaction, various catalysts were compared.[533] The best results were obtained with the complexes $[PdCl_2\{P(p\text{-}tol)_3\}_2]$ and $[PdCl_2(PPhMe_2)_2]$, both in the presence of $SnCl_2$. Some of the branched chain product is also formed. Other alkynes were studied, and the mechanism of Scheme 48 was suggested.

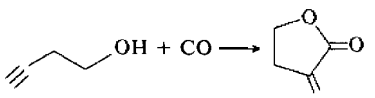
$$n\text{-}C_5H_{11}{\equiv}CH + CO + MeOH \rightarrow n\text{-}C_5H_{11}CH{=}CHCO_2Me \qquad (129)$$



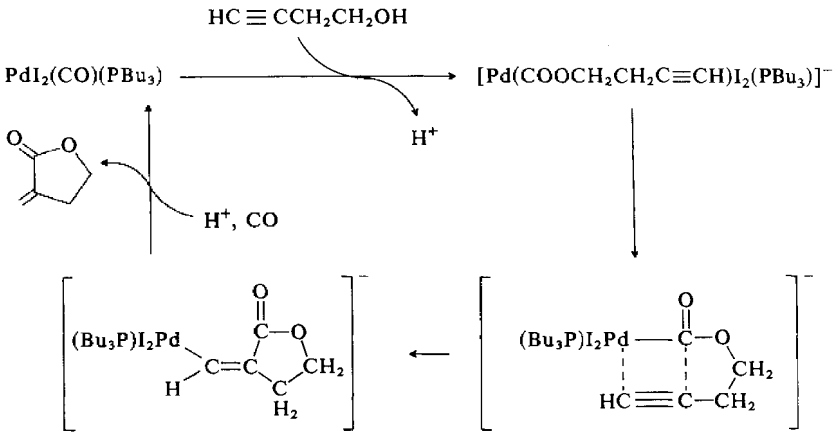
Scheme 48

In the hydroesterification of acetylene by complexes of the type $[PdX_2\{P(OR)_3\}_2]$ ($X = Cl^-$, Br^-, I^-, NCS^-; R = Me, Et, Pr^i) the catalytic activity decreased in the order $P(OMe)_3 > P(OEt)_3 > P(OPr^i)_3$. For $P(OPr^i)_3$ as phosphorus ligand the rates decreased in the order $NCS^- > I^- > Br^- > Cl^-$. For the two other phosphites the reverse order was found.[534]

The hydroesterification of alkynes has been adapted to ring-closure reactions, acetylenic alcohols cyclizing to give α-methylene lactones (equation 130.)[535] PdI_2 in the presence of PBu_3 was the catalyst. When the hydroxyl group was deuterated, the deuterium in the product occurred only in the methylene group. In presence of $SnCl_2$ the reactions were accelerated and coordination of the substrate to the palladium was found to be the rate determining step. In absence of $SnCl_2$, coordination of CO becomes rate determining. The reaction proceeds *via* an alkoxycarbonyl intermediate and the mechanism is given in Scheme 49.[536]

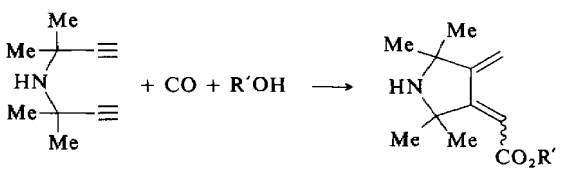


(130)



Scheme 49

This reaction has been used to prepare many α-methylene lactone derivatives.[537] The above alkyne carbonylations were all catalyzed by phosphorus ligand-containing complexes. Some phosphorus-free catalysts for these reactions are also known, such as $PdCl_2$ in presence of thiourea.[538] This catalyst system also effects ring closure of 1,6-diynes (equation 131).[539]



(131)

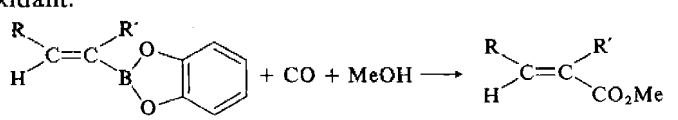
By use of stoichiometric quantities of $CuCl_2$, again in presence of a catalytic amount of $PdCl_2$, an oxidative carbonylation of alkynes to the corresponding esters has been achieved.[540] Sodium acetate was used as base. In its absence the reactions were no longer clean. The function of $CuCl_2$ and NaOAc is indicated in equations (132)–(134).

$$RC{\equiv}CH + CO + R'OH + PdCl_2 \rightarrow RC{\equiv}CO_2R' + 2HCl + Pd \quad (132)$$

$$Pd + 2CuCl_2 \rightarrow PdCl_2 + 2CuCl \quad (133)$$

$$NaOAc + HCl \rightarrow NaCl + AcOH \quad (134)$$

Another method for the preparation of acetylenic carboxylates involves the reaction of 1-alkenylboranes with CO and alcohols (equation 135). The alkenyl boranes are readily prepared from alkynes by addition of boranes. $PdCl_2$ was again the catalyst, with NaOAc as base and benzoquinone as oxidant.[541]

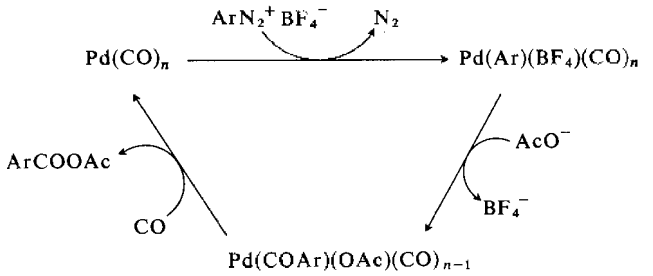


(135)

Arenediazonium salts can be carbonylated to give mixed anhydrides in the presence of NaOAc and catalytic amounts of $[Pd(OAc)_2]$. The mixed aryl-acetic anhydrides formed were generally hydrolyzed *in situ* and the free carboxylic acids were isolated. The carbonylation occurs according to equation (136).[542]

$$RN_2^+ + CO + AcO^- \rightarrow RCOOAc + N_2 \quad (136)$$

$[PdCl_4]^{2-}$ and $[Pd(DBA)_2]$ (**105**) were also used as catalyst, but the acetate was preferred. The initial palladium(II) complexes are readily reduced to palladium(0) in the reaction mixture. The mechanism proposed is given in Scheme 50.



Scheme 50

In some cases the mixed anhydrides were isolated for use as intermediates.[543] When tin compounds of the type R_4Sn (R = Me, Et, Ph) were introduced into reaction (136) in place of NaOAc, ketones were obtained in good yields.[544] The counter ion of the diazonium salt was important in these reactions: BF_4^- and PF_6^- were generally used; with Cl^-, very poor yields were achieved.

Palladium complexes catalyze the carbonylation of aromatic nitro compounds, giving isocyanates (equation 95). Initial studies were carried out using $[PdCl_2py_2]$ (**115**) as catalyst.[545] The reactions require both high temperature and CO pressure. Other complexes used include $[Pd(DBA)_2]$ (**105**), $[PdCl_3(CO)]^-$, $[Pd_2Cl_4(CO)_2]^{2-}$, $[PdCl_4]^{2-}$, $[Pd_2Cl_6]^{2-}$, $[Pd_2Br_6]^{2-}$, $[PdCl_2L_2]$ (L = PhCN, Pr^nCN) and $[PdCl_2L']_2$ (L' = styrene, cyclohexene, Bz_2S).[546-548]

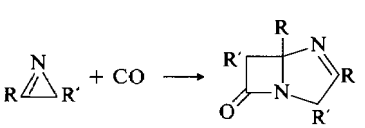
1,3-Diaryltriazenes can be carbonylated with loss of nitrogen to give aryl amides, using $[PdCl_2(PPh_3)_2]$ as catalyst (equation 137).[549] The mechanistic details are at present uncertain. The reaction of an aromatic nitro compound and an aryl amine with CO catalyzed by complex (**106**) in the presence of PPh_3 or by the bromo complex (**108**) or its chloro analogue gives rise to diarylureas (equation 138).[550]

$$ArNHN{=}NAr + CO \rightarrow ArCONHAr + N_2 \quad (137)$$

$$ArNH_2 + ArNO_2 + 3CO \rightarrow ArNHCONHAr + 2CO_2 \quad (138)$$

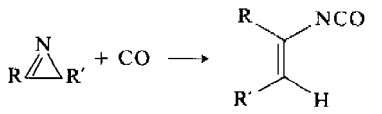
The reaction required the presence of a base and of chloride ion, though both could be used in less than the stoichiometric amount. When $P(o\text{-tol})_3$ or $P(OPh)_3$ was used in place of PPh_3, reaction (138) did not occur. The mechanism of the reaction is unknown. At normal temperature and CO pressure a direct carbonylation on aniline to diphenylurea has been reported.[551] The catalyst was $PdCl_2$ in presence of Na_2HPO_4.

Aziridines undergo carbonylation with ring opening in presence of palladium(0) complexes. The nature of the product is dependent on the ligands used.[552,553] With $[Pd(PPh_3)_4]$ (**103**) as catalyst a ring-fused β-lactam is obtained (equation 139).

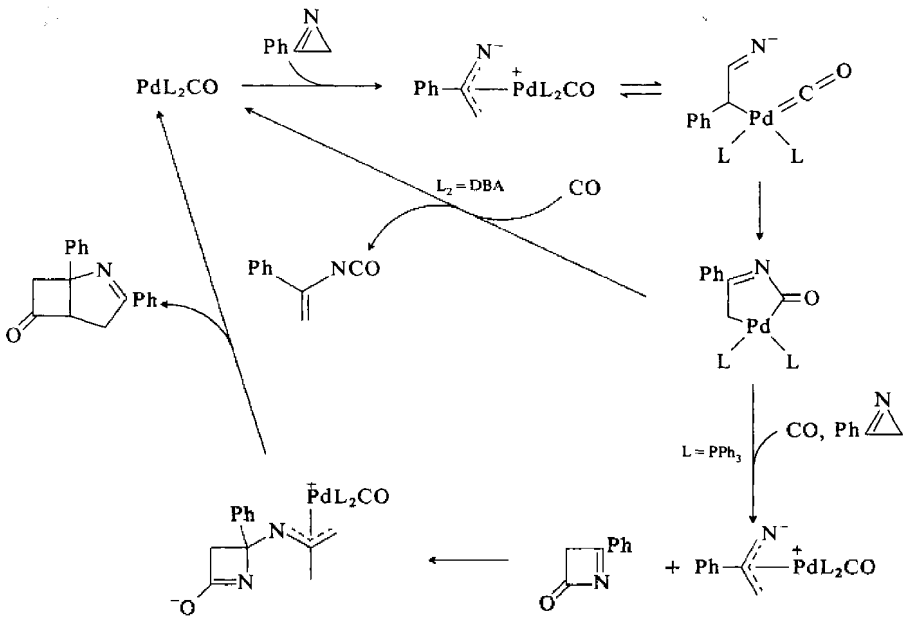


(139)

The use of polar solvents or ligands such as 2,2'-bipyridyl decreased the yield. The complex $[Pd(diphos)_2]$ (**104**) was inactive, as were $[Ni(PPh_3)_4]$ and $[Pt(PPh_3)_4]$. Complex (**103**) was believed to give the carbonyl $[Pd(CO)(PPh_3)_3]$ prior to commencement of catalytic action. When $[Pd(DBA)_2]$(**105**) was used as catalyst, reaction (139) did not occur at all, the sole product being the vinyl isocyanate formed according to equation (140). A possible mechanism for these reactions is shown in Scheme 51.



(140)



Scheme 51

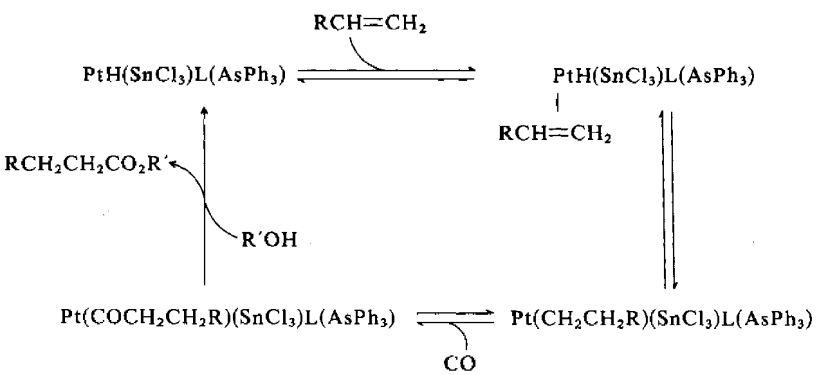
Reviews are available on the palladium-catalyzed carbonylation of organic halides,[554] dienes[555] and mixtures of alkenes and organic halides.[556]

61.2.5.8 Platinum

Platinum complexes have so far proved to be of only limited value as carbonylation catalysts. H_2PtCl_6 in the presence of $SnCl_2$ acts as a hydroesterification catalyst for terminal alkenes (equation 141).[557]

$$RCH{=}CH_2 + CO + R'OH \rightarrow RCH_2CH_2CO_2R' \qquad (141)$$

$[PtCl_6]^{2-}$ could be used but $[PtCl_2(PPh_3)_2]$ was inactive. Good selectivity to the linear ester was obtained. It was subsequently shown that other Group V ligands are far superior to PPh_3 in these reactions. Using the complexes $[PtCl_2L_2]$ ($L = AsPh_3$, $AsClPh_2$, $P(OPh)_3$), all in the presence of $SnCl_2$, high selectivities and conversions to linear esters could be obtained with both short- and long-chain terminal alkenes.[558] Replacement of the alcohol by water gave the carboxylic acids. Other phosphorus, arsenic and antimony ligands were studied, but they were less effective. The reactions required raised temperature and especially raised CO pressure. The mechanism proposed for the formation of the linear esters is given in Scheme 52.



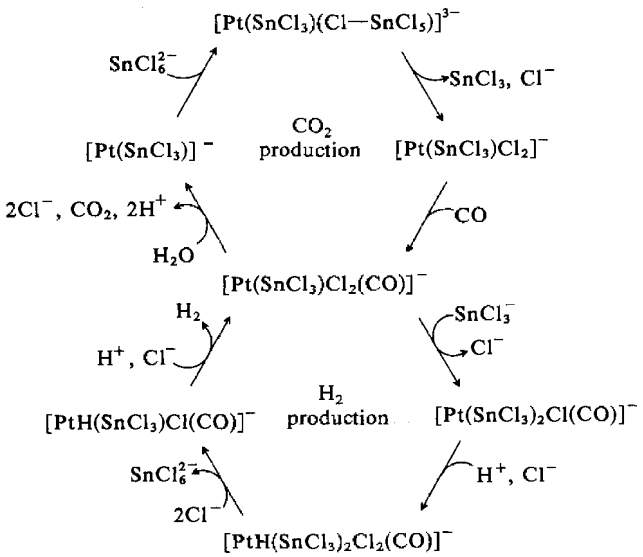
($L = SnCl_3^-$, Cl^-, CO or solvent)

Scheme 52

$[PtCl_4]^{2-}$ in the presence of $SnCl_2$ acts as a catalyst for the water-gas shift reaction (equation 70).[559] Evidence was found for the presence of the complexes $[PtCl(SnCl_3)_2CO]^-$ and $[PtCl_2(SnCl_3)CO]^-$ in the reaction mixture. The former was believed to be responsible for the production of hydrogen and the latter for that of carbon dioxide, the two complexes being related in solution by a stoichiometric reaction or perhaps by a direct ligand substitution. In the absence of $SnCl_2$ the catalytic activity decreased markedly. The isolation of salts of the $[SnCl_6]^{2-}$ ion indicated that tin was involved in the redox chemistry and not present just as a ligand. The water-gas shift reaction can occur in two separate steps if the tin(II)/tin(IV) couple participates (equations 142, 143). Both of these reactions would be catalyzed by platinum complexes. The proposed mechanism is given in Scheme 53.

$$2H^+ + SnCl_3^- + 3Cl^- \xrightarrow{[Pt]} H_2 + [SnCl_6]^{2-} \quad (142)$$

$$CO + H_2O + [SnCl_6]^{2-} \xrightarrow{[Pt]} CO_2 + 2H^+ + SnCl_3^- + 3Cl^- \quad (143)$$



Scheme 53

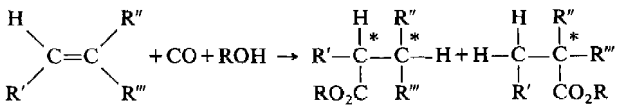
$[PtCl_2(PPh_3)_2]$ in the presence of $SnCl_4$ and Et_3N, both in catalytic amounts, catalyzes the reduction of nitroarenes to aniline derivatives by CO and water (equation 74).[560] $SnCl_2$ was less effective. The reaction requires raised temperature and CO pressure. If alcohols were used in the same reaction in place of water, alkyl aryl carbamates were produced (equation 144).[561] The catalyst precursor was again $[PtCl_2(PPh_3)_2]$ with $SnCl_4$ and Et_3N.

$$PhNO_2 + 3CO + EtOH \rightarrow PhNHCO_2Et + 2CO_2 \quad (144)$$

Reviews relevant to Section 61.2.5 and not pertaining to individual metals are collected here. An early review[562] and some more recent general ones on carbonylation[563–566] are available. Other reviews cover insertion reactions of CO,[567–569] hydrogenation of CO,[570,571] ring-closure reactions[572] and the water-gas shift.[573]

61.2.5.9 Asymmetric Carbonylation

So far, very little work has been carried out on asymmetric carbonylation. Existing studies all concern the hydroesterification of alkenes (equation 145). Depending on the structure of the alkene and the regioselectivity of the reaction, one or two asymmetric carbon atoms may be present in the product (equation 145).[574]



(145)

$PdCl_2$ in the presence of (−)-DIOP (**49**) catalyzes the reaction of butene and styrene derivatives with CO and alcohols. The reactions require high temperature and CO pressure.[574] Using α-methylstyrene and isopropanol, a best optical yield of 14% was obtained for isopropyl 3-phenylbutanoate, which is the major product. In a more detailed study of this reaction using the same catalyst precursor as above, the optical yield was found to increase with CO pressure and to depend on the alcohol used.[575] The optimum ratio of DIOP to $PdCl_2$ as regards the optical yield was 0.4, though the rate was much reduced under these conditions. $PdCl_2$ alone did not catalyze the reaction. The best optical yield obtained was 59%, in the formation of *t*-butyl 3-phenylbutanoate. When the DIOP/$PdCl_2$ ratio was varied in the presence of sufficient PPh_3 to maintain a phosphorus/palladium ratio of 2, the optical yield passed through a broad maximum of about 51% in the range DIOP/$PdCl_2$ = 0.3–0.7.[576] Ethanol replaced *t*-butanol in this work. These results were interpreted as indicating that, at such DIOP/Pd ratios, DIOP functioned as a monodentate ligand.

Again using α-methylstyrene and isopropanol, the ligands (**117a**), (**117b**), (**118a**), (**118b**), (**119a**) and (**119b**) have been compared (Figure 2). [$PdCl_2(NCPh)_2$] was the palladium source.[577]

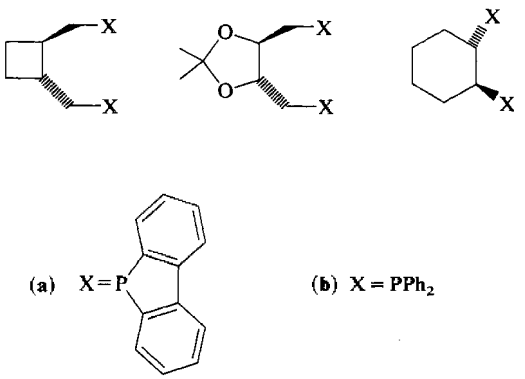


Figure 2

The preferred configuration of the product was the same for all the ligands, contrary to the behaviour observed when they were used in rhodium-catalyzed hydroformylation. The best results were obtained with (**117a**) and (**118a**). With these two ligands it was not necessary to use low ratios of ligand to palladium or very high pressures, as had been found essential with (**118b**).[575] A best optical yield of 69% was achieved using (**118a**).

With [$Pd(DBA)_2$] (**105**) in the presence of (+)-neomenthyldiphenylphosphine, the hydroesterification of styrene with CO and methanol gave a best optical yield of 52% for the methyl 2-phenylpropionate formed.[578] The reactions were carried out in presence of trifluoroacetic acid. Other acids were of far lesser value. It was believed that the complex [$PdH(O_2CCF_3)PPh_2$(neomenthyl)] was formed.

The precise origin of the stereoselectivity in these reactions is not known at present. The acyl mechanism has generally been assumed, rather than the alkoxycarbonyl one (see Section 61.2.5.8) and it seems reasonable that asymmetric induction must have taken place prior to or during the CO insertion reaction. A review of asymmetric carbonylation is available.[579]

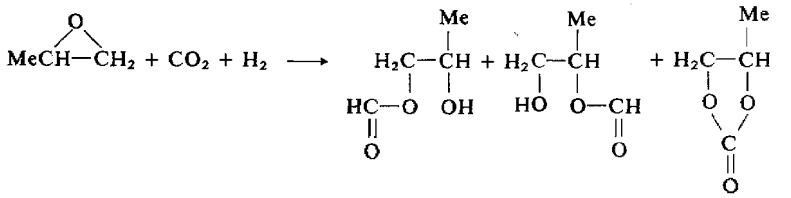
61.2.6 CARBON DIOXIDE

61.2.6.1 Ruthenium

Carbon dioxide reacts with silanes in the presence of ruthenium complexes to give silyl formates (equation 146). The hydride $[Ru_3H(CO)_{11}]^-$ catalyzes the reaction under CO_2 pressure and at raised temperature. From the reaction mixture the complex $[Ru_3H(SiEt_3)_2(CO)_{10}]^-$ was isolated. This complex was a more efficient catalyst for the reaction than $[Ru_3H(CO)_{11}]^-$.[580] Using $MeEt_2SiH$ instead of Et_3SiH, reaction (146) is also catalyzed by $[RuCl_2(PPh_3)_3]$ (**2**) and $[Ru(H)_2(PPh_3)_4]$ (**6**).[581] When $Me(MeO)_2SiH$ was used the reaction was only stoichiometric. The mechanism of the reaction is not known.

$$CO_2 + Et_3SiH \rightarrow Et_3SiO\overset{O}{\overset{\|}{C}}H \qquad (146)$$

Complex (**2**) also catalyzes the reaction of propylene oxide with CO_2 (equation 147).[582] The lactone (**122**) was the major product. Complex (**6**) catalyzes the formation of ethyl formate from ethanol, CO_2 and H_2.[583]



(147)

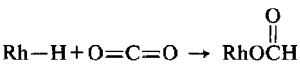
(120) (121) (122)

61.2.6.2 Cobalt, Rhodium and Iridium

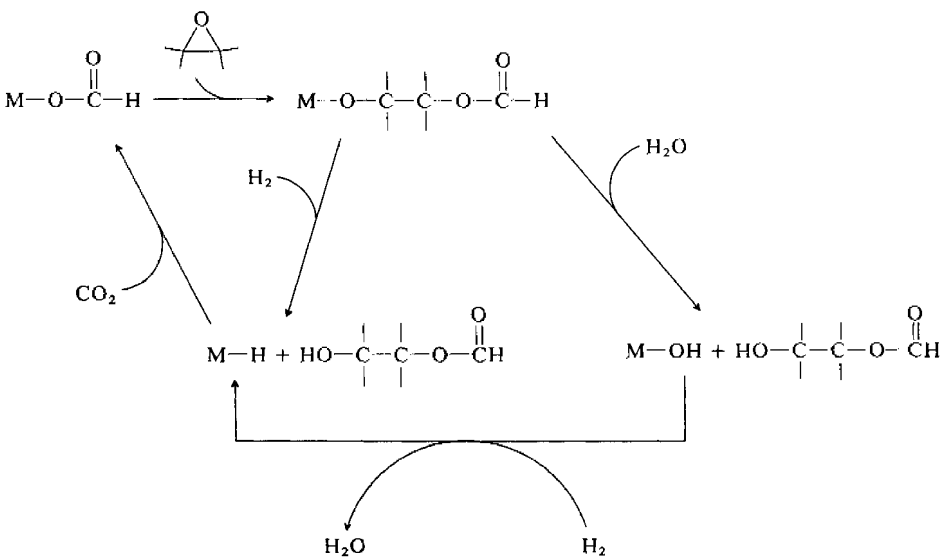
$[RhCl(PPh_3)_3]$ (**23**) catalyzes the reaction of ethylene with CO_2 according to equation (148).[584] The reactions were carried out at very high temperature and pressure. A mole of hydrogen is required for product formation but hydrogen was not added to the reaction mixture. Water was used as solvent, generally in the presence of mineral acid, and ethanol was formed as a by-product, presumably by direct addition of water to ethylene. One possible source of the hydrogen would be a transfer hydrogenation using the ethanol formed.

$$C_2H_4 + CO_2 + [H_2] \rightarrow EtCO_2H \qquad (148)$$

Complex (**23**) also catalyzes reaction (147). In addition to the products (**120**)-(**122**), the diformate ester of 1,2-propylene glycol was also formed.[582] Other epoxides were studied and the complex $[CoCl(PPh_3)_3]$ catalyzed the formation of the lactone (**122**) only. Formate complexes were believed to be present, resulting from the insertion of CO_2 into a rhodium-hydride bond (equation 149). The formate complex then initiates the catalytic cycle. The general mechanism given in Scheme 54 was proposed for the reaction.

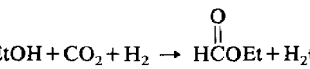


(149)



Scheme 54

CO_2 reacts with ethanol and H_2 in presence of a tertiary amine to give ethyl formate (equation 150).[583] The cobalt complexes $[CoH(diphos)_2]$ (**123**) and $[Co(HCO_2)(PPh_3)_3]$ (**124**) gave only low turnover numbers, with complex (**123**) being the better catalyst of the two. $[RhCl(PPh_3)_3]$ (**23**) and $[Ir(H)_3(PPh_3)_3]$ (**38**) were more efficient. The presence of the base was essential but its function is unknown.



(150)

61.2.6.3 Nickel, Palladium and Platinum

When the nickel complexes $[NiX_2(PPh_3)_2]$ (X = Cl, Br) are reduced electrochemically in the presence of CO_2 and aryl halides, aryl carboxylate anions are formed.[585] The reduction leads to nickel(0) complexes which then undergo oxidative addition of the aryl halide followed by insertion of CO_2. Further reduction then gives the product and regenerates nickel(0) (Scheme 55).

$$Ni^{II} + 2e \xrightarrow{\text{electrode}} Ni^0 \quad (151)$$

$$Ni^0 + ArX \rightarrow Ni^{II}X(Ar) \quad (152)$$

$$Ni^{II}X(Ar) + CO_2 \rightarrow Ni^{II}X(O_2CAr) \quad (153)$$

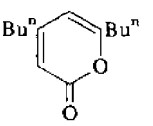
$$Ni^{II}X(O_2CAr) + 2e \xrightarrow{\text{electrode}} Ni^0 + X^- + ArCO_2^- \quad (154)$$

Scheme 55

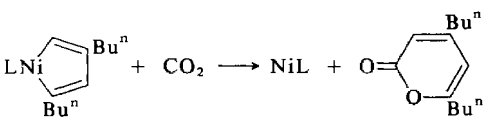
Equations (151)–(154) constitute the catalytic cycle. The carboxylate anions coordinate strongly to nickel(II), and limit the reaction to low turnover numbers.

$[Ni(cod)_2]$ in the presence of the diphosphines $Ph_2P(CH_2)_nPPh_2$ ($n = 1$–4) catalyzes the reaction of 1-hexyne with CO_2 to give the lactone (**125**) in addition to products not containing CO_2 (equation 155).[586] The best results regarding the phosphorus ligands were obtained with $n = 4$. The reaction was believed to proceed *via* a metallocycle formed by dimerization of the 1-hexyne at a nickel(0)–phosphine complex (equation 156).

$$2Bu^nC{\equiv}CH + CO_2 \longrightarrow \quad (155)$$

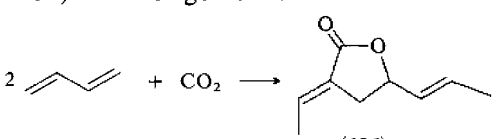


(**125**)



(156)

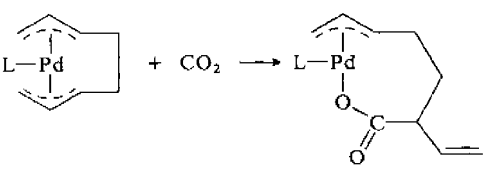
The reaction of CO_2 with 1,3-butadiene leads to the formation of 2-ethylidene-5-hepten-4-olide (**126**) in low yields (equation 157).[587,588] Oligomers of butadiene are the major products.



(157)

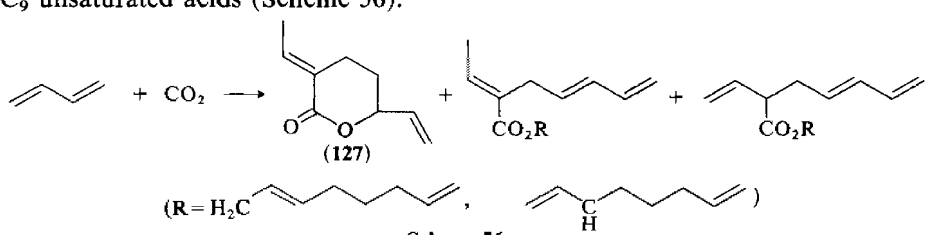
(**126**)

Polar, aprotic solvents such as DMF were necessary for the formation of (**126**). $[Pd(diphos)_2]$ (**104**) gave the best performance as catalyst. Using $[Pd(DBA)_2]$ (**105**) as palladium source, a number of mono- and bi-dentate nitrogen, phosphorus and arsenic ligands were investigated and $Me_2PCH_2CH_2PMe_2$ was found to be nearly as effective as diphos. The reaction of CO_2 with a bis(η^3-allyl) complex of palladium was believed to be a key step in the process (equation 158).



(158)

When monodentate phosphine ligands were present, either in absence of solvent or in a non-polar solvent, butadiene and CO_2 reacted to give the lactone (*E*)-ethylidenehept-6-en-5-olide (**127**) and esters of C_9 unsaturated acids (Scheme 56).[589,590]

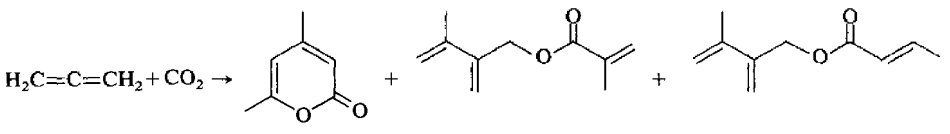


(**127**)

Scheme 56

The 2-methylallyl complex [Pd(OAc)(η^3-C_4H_7)] in the presence of various phosphines was used as catalyst. The product selectivity obtained was generally poor. With PCy_3 and PPr^i_3 the lactone (**127**) was the major product. PMe_2Ph, PBz_3 and PPh_3 gave predominantly esters. Formation of oligomers of butadiene occurred in all cases and when PEt_3, PBu^t_2Ph, $PMePh_2$ and P(*o*-tol)$_3$ were used the oligomers were the major products.[590] The mechanism was again believed to involve CO_2 insertion as in equation (158). Comparison of the product distributions with the cone angles[591] and basicities[592] of the phosphine ligands used suggested that PCy_3 and PPr^i_3 favoured lactone formation as a result of electronic effects.[590]

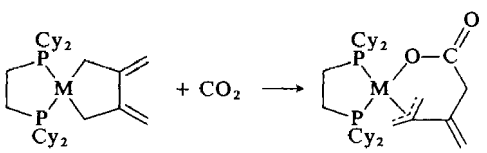
Behaviour similar to that of butadiene was observed in the reaction of allene with CO_2, both esters and a lactone being formed.[593] The catalyst was prepared *in situ* from $Cy_2PCH_2CH_2PCy_2$ and [Pd(η^3-C_3H_5)$_2$]. Scheme 57 gives the products formed from CO_2. Allene oligomers also occur.



(**128**)

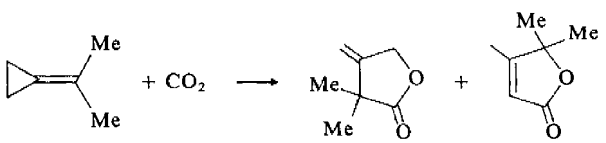
Scheme 57

The use of [Pd(DBA)$_2$] (**105**) as palladium source or the use of other phosphine ligands led to no formation of lactone (**128**). The product selectivity was very poor, and (**128**) was never the major product. The CO_2 fixation step may be as shown in equation (159) by analogy with other reactions.[593]



(159)

With methylenecyclopropane derivatives, CO_2 again reacted to give lactones (equation 160).[594] With complex (**105**) and PPh_3 as catalyst precursor, (**129**) was formed. Using [Pd(diphos)$_2$] (**104**) both (**129**) and (**130**) were obtained with the latter as major product.



(160)

Complex (**104**) in presence of tertiary amines catalyzes the formation of alkyl formates from alcohols, CO_2 and H_2 according to equation (150).[583] Other catalysts for the same reaction include [$PdCl_2(Ph_2PCH_2PPh_2)$], [$Pd(Ph_2PCH_2PPh_2)_2$], [$Pd(Ph_2PCH_2PPh_2)EtOH)_x$]$^{2+}$ and [$Pd_2Cu_2Cl_6(Ph_2PCH_2PPh_2)_3$].[595] Three general reviews of catalytic reactions of carbon dioxide[380,596,597] and one review on its reactions with hydrogen[598] are available.

61.2.7 HYDROGEN CYANIDE

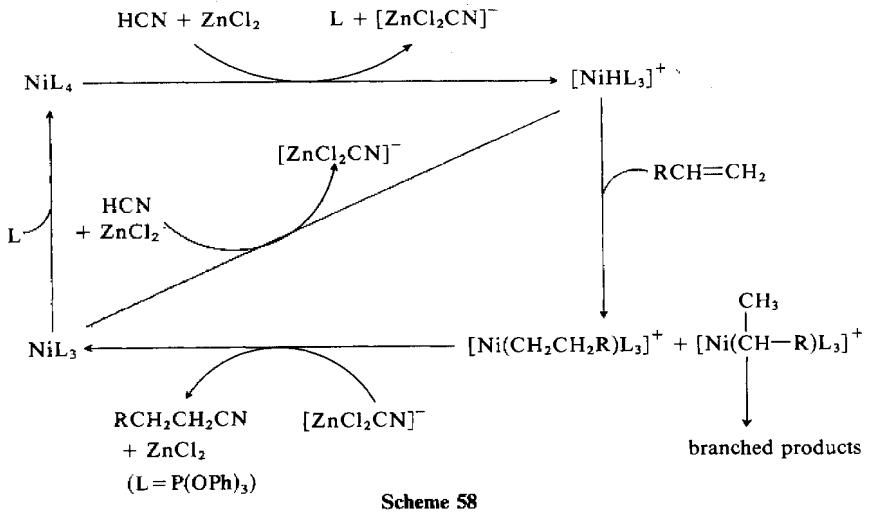
61.2.7.1 Nickel

Addition of hydrogen cyanide to a terminal alkene is catalyzed principally by nickel and palladium complexes. The reaction may give either linear or branched products (equation 161). The reaction is of considerable industrial interest. A review on the earlier work is available.[599]

$$RCH{=}CH_2 + HCN \rightarrow RCH_2CH_2CN + RCH(CN)Me \qquad (161)$$

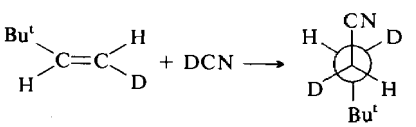
The hydrocyanation of 1-hexene catalyzed by [Ni{P(OPh)$_3$}$_4$] has been studied.[600] Isomerization of the alkene accompanies the reaction. Best rates were obtained in the presence of excess $P(OPh)_3$ and a Lewis acid ($ZnCl_2$). The excess $P(OPh)_3$ was believed to suppress the formation of the cyano complex [Ni(CN)$_2${P(OPh)$_3$}$_2$], which does not catalyze hydrocyanation. $ZnCl_2$ increases

the acidity of HCN, facilitating its oxidative addition to nickel(0) and it possibly also acts as a cyanide acceptor. The proposed mechanism is given in Scheme 58.



Scheme 58

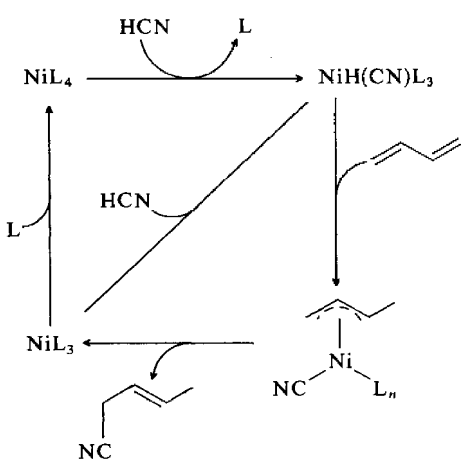
It has been shown that the addition of HCN to the alkene occurs in a *cis* (suprafacial) manner.[601] This was achieved by the addition of DCN to (*E*)-1-deuterio-3,3-dimethylbut-1-ene, catalyzed by [Ni{P(OPh)$_3$}$_4$] (**131**) (equation 162). This requires retention of configuration at the alkyl carbon atom during the reductive elimination of the product from the intermediate nickel(II)-alkyl complex. A cyanoalkyl complex [Ni(CN)(CHDCHBu^t){P(OPh)$_3$}$_2$] was proposed as the key intermediate in this process.



(162)

The hydrocyanation of butadiene is an important industrial route to adiponitrile (equation 163).[602] Again, complex (**131**) is used as the catalyst for the reaction. The hydrocyanation of dienes proceeds mainly by 1,4-addition and η^3-allyl complexes are believed to be intermediates (Scheme 59).[603] The 1-cyano-2-butene is then isomerized to 1-cyano-3-butene which undergoes further hydrocyanation to give adiponitrile.[601-603]

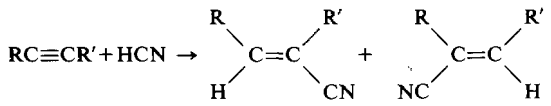
$$CH_2{=}CHCH{=}CH_2 + 2HCN \rightarrow NC(CH_2)_4CN \qquad (163)$$



Scheme 59

Complex (**131**) catalyzes the hydrocyanation of both mono- and di-substituted alkynes and, here again, *cis* addition of HCN occurs.[604] The monosubstituted alkynes generally give linear

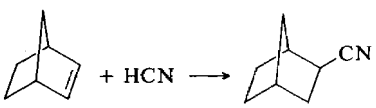
nitriles as products with high selectivity (equation 164). As is often the case in hydrocyanation, this reaction was also carried out in the presence of excess of the phosphite ligand.



(164)

61.2.7.2 Palladium

Hydrocyanation is also catalyzed by $[Pd(PPh_3)_4]$ (**103**) and $[Pd\{P(OPh)_3\}_4]$ (**132**), again in both cases in the presence of excess ligand.[604] Complex (**132**) is an effective catalyst for the addition of hydrogen cyanide to cyclic monoenes and dienes such as norbornene and norbornadiene;[605,606] ethylene also reacted readily. The product obtained from norbornene was the *exo* isomer (equation 165). When norbornadiene was the substrate, some of the *endo* product was formed.[605]



(165)

The stereochemistry of palladium-catalyzed hydrocyanation has been studied further using $[Pd(DIOP)_2]$ (**133**) as catalyst.[607] It was shown that the addition of HCN to both cyclic and acyclic alkenes is *cis*. The mechanism is believed to be the same as for the nickel-catalyzed reaction (Scheme 58).

Asymmetric hydrocyanation has now been achieved using norbornene and norbornadiene as substrates. The reduction of either $[PdCl_2(+)\text{-DIOP}]$ or $PdCl_2$ in presence of (+)-DIOP led to a palladium(0) species formulated simply as [Pd(+)-DIOP]. This gave, in reaction (164), an optical yield of 30% for the 2-*exo*-cyanonorbornane formed. Norbornadiene with the same catalyst gave 2-*exo*-cyanonorborn-5-ene with an optical purity of 17%. When the ligand CHIRAPHOS (**51**) was used, the catalytic activity was greatly diminished.[608,609] In addition to the review of the early work already mentioned, two more recent reviews of hydrocyanation have appeared.[610,611]

61.2.8 ETHYLENE, PROPYLENE, ACETYLENE AND PROPYNE

This section covers reactions of the above four molecules which have not already been dealt with in one of the preceding sections.

61.2.8.1 Rhenium

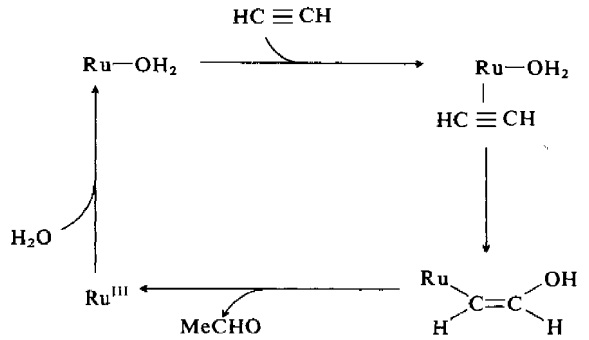
$ReCl_5$ has been found to act as a Friedel–Crafts catalyst for the alkylation of benzene with ethylene. Ethylbenzene, *s*-butylbenzene and hexaethylbenzene were formed.[612] When propylene was used in place of ethylene, cumene and di-, tri- and tetra-isopropylbenzenes were obtained.[613] Ethylbenzene and anisole were also alkylated with ethylene. A carbonium ion mechanism was proposed, in some cases with dimerization of ethylene preceding alkylation.

61.2.8.2 Ruthenium

In aqueous 5M HCl, solutions of ruthenium chloride catalyze the hydration of acetylene, giving acetaldehyde (equation 166).[614] Propyne reacted to give acetone. The reaction is inhibited by high or low chloride concentrations. The mechanism proposed is given in Scheme 60.

$$HC{\equiv}CH + H_2O \rightarrow MeCHO \qquad (166)$$

The complexes $[RuCl_4(H_2O)_2]^-$ and $[RuCl_5(H_2O)]^{2-}$ were responsible for the catalytic activity. The inhibition by excess chloride ion was attributed to the formation of $[RuCl_6]^{3-}$. At lower chloride ion concentration the reduction in rate was caused by the formation of neutral or cationic complexes, which are inert to ligand substitution reactions. These reactions could be carried out at normal pressure and slightly raised temperature.



Scheme 60

Methyl formate can be made to add to ethylene in the presence of $[RuCl_2(PPh_3)_3]$ (**2**) or $RuCl_3$ as catalyst (equation 167).[615] Other formates react less well. The mechanism is believed to involve oxidative addition of the C—H bond of the formate residue to ruthenium (Scheme 61).

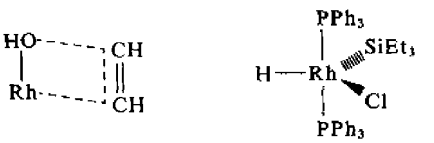
$$C_2H_4 + HCOMe \rightarrow EtCOMe \qquad (167)$$



Scheme 61

61.2.8.3 Rhodium

Reaction (166) is also catalyzed by acidic rhodium chloride solutions under similar conditions to those used for ruthenium. Aquachloro complexes were again implicated and the most active species was $[RhCl_5(H_2O)]^{3-}$. The hydration step was thought to involve a four-centred transition state (**134**).[616] Here also, inhibition at low and high chloride ion concentration occurred.



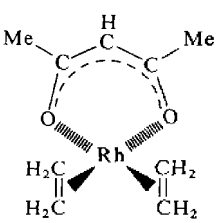
(**134**) (**135**)

When ethylene was passed into a basic solution of $Hg(OAc)_2$ containing a catalytic amount of $[Rh_2(OH)_3(C_5Me_5)_2]^+$, ethanol was formed.[617] It appears that mercury salts of the type $HOCH_2CH_2HgOAc$ are formed in a stoichiometric reaction so that this is not strictly a catalytic activation of ethylene by the rhodium complex.

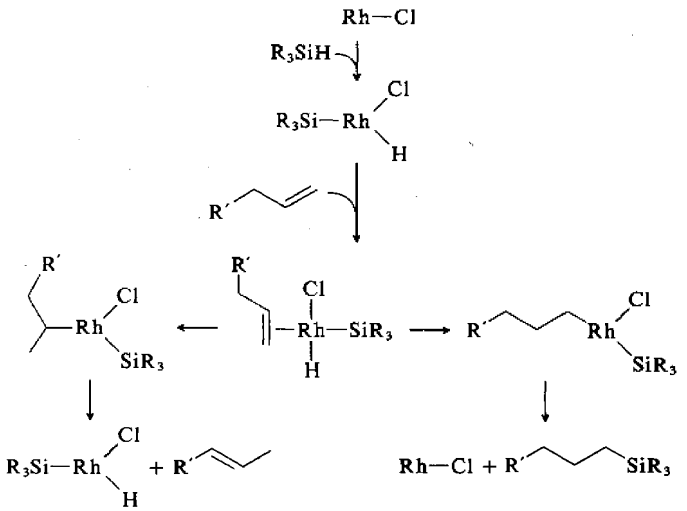
$[RhCl(PPh_3)_3]$ (**23**) catalyzes the hydrosilylation of propylene (equation 168).[618] The silyl complex $[RhH(Cl)(SiEt_3)(PPh_3)_3]$ (**135**) was present in the reaction mixture, but was not thought to be involved in the catalytic cycle. Small amounts of oxygen or peroxide were necessary for the hydrosilylation to proceed and this was attributed to the generation of coordinative unsaturation by removal of triphenylphosphine as the oxide.

$$H_3CCH{=}CH_2 + HSiEt_3 \rightarrow CH_3CH_2CH_2SiEt_3 \qquad (168)$$

Isomerization of the alkene occurred, even when hydrosilylation was not taking place. Propylene was used to render this insignificant. The mechanism is thought to be as shown in Scheme 62.

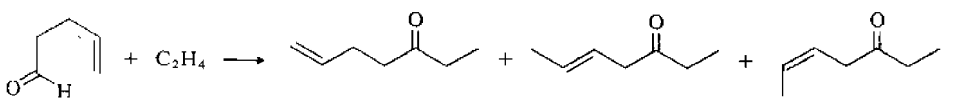


(**136**)



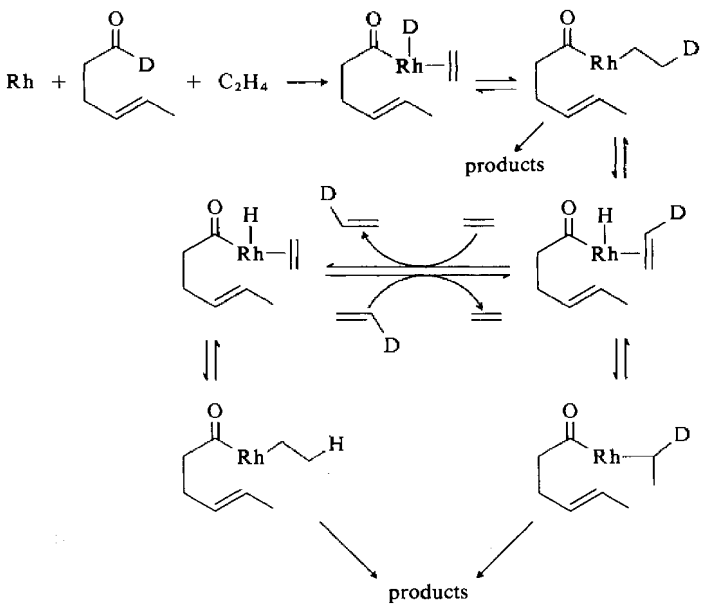
Scheme 62

In the presence of catalytic amounts of [Rh(acac)(C_2H_4)$_2$] (**136**), ethylene reacts with 4-penten-1-al with insertion into the aldehyde C—H bond (equation 169).[619]



(169)

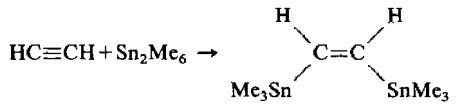
The reaction occurs slowly at normal temperature, but other unsaturated aldehydes also reacted. When 4-hexenal-1-*d* was used, the deuterium was found to be distributed over both carbon atoms of the former ethylene molecule. In addition, deuterium was found in the recovered gaseous ethylene, whilst some of the 6-octen-3-one product was deuterium-free. These observations are readily explained by the mechanism given in Scheme 63, in which alkene insertion and hydride elimination are faster than the reductive elimination of the final product.



Scheme 63

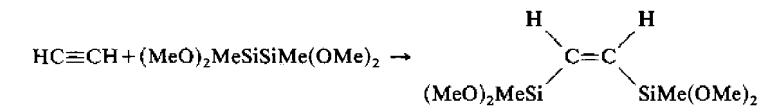
61.2.8.4 Palladium

[Pd(PPh_3)$_4$] (**103**) catalyzes the hydrosilylation of both ethylene and propylene by trichlorosilane.[620] The same complex also catalyzes reaction (170).[621]

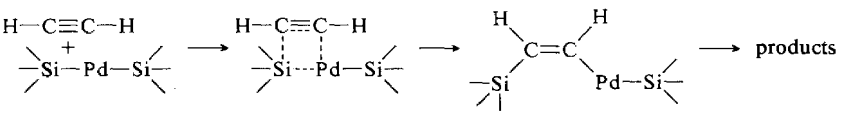


(170)

Isomerization of the product to the (*E*) isomer eventually occurs when the reaction is carried out at raised temperature, but at 25 °C the pure (*Z*) isomer is obtained. Complex (**103**) also catalyzes the addition of disilanes such as $(MeO)Me_2SiSiMe_2(MeO)$ and $(MeO)_2MeSiSiMe(MeO)_2$ to acetylene (equation 171).[622] Again, the (*Z*) isomer is formed with high selectivity. Scheme 64 gives the mechanism outlined to explain the regioselectivity of the reaction.

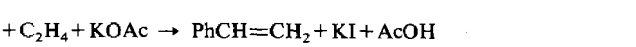


(171)



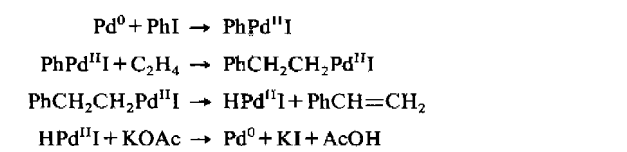
Scheme 64

A number of methods are now available for the palladium-catalyzed arylation of alkenes. Mizoroki *et al.* showed that, in the presence of $PdCl_2$, iodobenzene reacted with ethylene to give styrene.[623] These reactions require a stoichiometric amount of base to neutralize the hydriodic acid formed (equation 172).



(172)

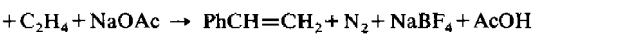
Propylene gave both 1-phenyl- and 2-phenyl-propylene. High temperature was required and a slightly raised pressure of the gas was used. On the basis of known stoichiometric reactions of palladium complexes the mechanism given in Scheme 65 was proposed.[624]



Scheme 65

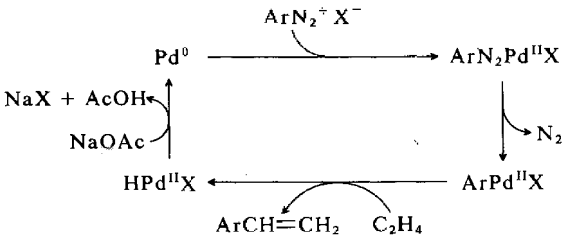
Using $[Pd(OAc)_2(P\text{-}o\text{-}tol)_2]$ as catalyst, aryl bromides can be used to arylate ethylene.[625] The reaction was shown to be more complex than was originally thought. The styrene derivatives formed could undergo a second arylation, leading to *trans*-stilbenes. The product selectivity could be controlled within certain limits by varying the ethylene pressure, higher pressures favouring the formation of styrene derivatives.[625] If stilbene derivatives are to be obtained, the reactions are best carried out under normal pressure of ethylene.[626] Further, these arylations are greatly assisted by choice of an appropriate combination of solvent and base, DMF and NaOAc being generally preferred. In this way, turnover numbers of over 18 000 could be obtained in the arylation of ethylene.[626]

Another method for the arylation of ethylene involves its reaction with arenediazonium salts (equation 177). $[Pd(DBA)_2]$ (**105**) was used as catalyst for the reaction.[627] These reactions can be carried out at room temperature, unlike the reactions of aryl bromides above. At ethylene pressures of 0.6–0.8 MPa, styrene derivatives were obtained in good yields. $[Pd(PPh_3)_4]$ (**103**) and $[Pd(DBA)_2]$ (**105**) plus diphos were also used as catalysts, but were less effective than complex (**105**) alone. The mechanism proposed is similar to that for arylation with aryl bromides and is given in Scheme 66.[628]



(177)

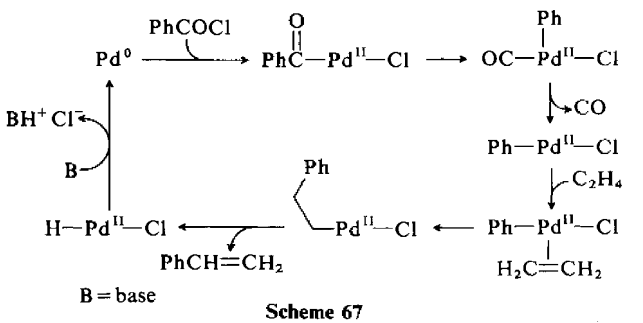
A third method for the palladium-catalyzed arylation of ethylene involves aroyl chlorides as the source of the aryl group and is accompanied by decarbonylation (equation 178).[629] $[Pd(OAc)_2]$



Scheme 66

(**106**) was used as catalyst. As with the aryl bromides,[625,626] stilbene derivatives are formed selectively under normal pressure of ethylene and styrene derivatives predominate at higher pressures. These reactions again require high temperature. Tertiary amines were the preferred bases, with *N*-benzyldimethylamine giving the best results. The mechanism involves decarbonylation of the aroyl chloride followed by arylation of the alkene (Scheme 67).[630]

$$PhCOCl + C_2H_4 + PhCH_2NMe_2 \rightarrow PhCH{=}CH_2 + CO + PhCH_2N^+HMe_2\,Cl^- \quad (178)$$



Scheme 67

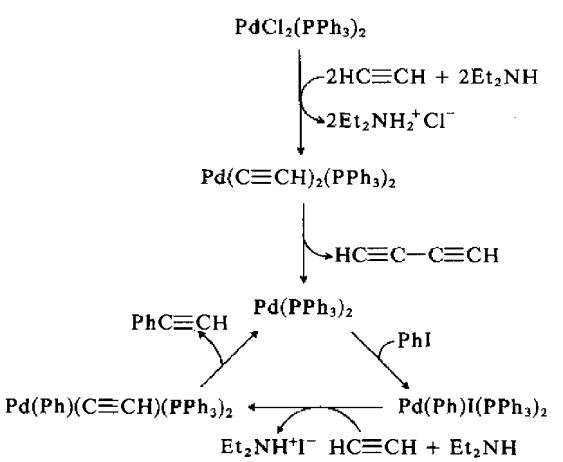
Where palladium(II) complexes are used as precursors in the above reactions, the palladium(0) species needed to initiate catalysis are generated by a stoichiometric reaction with alkene and base (equation 179).

$$Pd^{II}X_2 + C_2H_4 + B \rightarrow Pd^0 + CH_2{=}CHX + BH^+\,X^- \quad (179)$$

Vinyl halides also enter into palladium-catalyzed reactions with ethylene. This will be dealt with under vinyl halides in Section 61.2.9.5.

Acetylene can be made to react with aryl iodides in the presence of $[PdCl_2(PPh_3)_2]$ and CuI as catalyst (equation 180).[631] The potential intermediate, phenylacetylene, was not observed. (*E*)-2-Bromostyrene and 2-bromopyridine also underwent the reaction. The initial reduction of palladium(II) to palladium(0) is believed to involve the coupling of two moles of acetylene. The precise mechanism is not known, but the reaction is thought to proceed according to Scheme 68.

$$2PhI + HC{\equiv}CH + 2Et_2NH \rightarrow PhC{\equiv}CPh + 2Et_2NH_2^+\,I^- \quad (180)$$



Scheme 68

The phenylacetylene formed would then re-enter the catalytic cycle for the second arylation. CuI is believed to assist the formation of the alkynylpalladium complexes. $[Pd(PPh_3)_4]$ (**103**) and $[PdCl_2(diphos)]$ in the presence of CuI also catalyze the reaction, which requires only normal temperature and acetylene pressure.

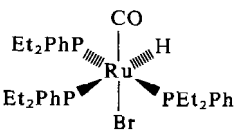
61.2.9 OTHER SMALL MOLECULES

Small molecules such as water, ammonia, the simple alcohols and amines and others have been dealt with in connection with the preceding sections. Those not so treated are covered here.

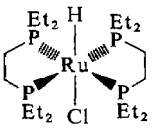
61.2.9.1 Formic Acid

Transition metal complexes catalyze the decomposition of formic acid according to equation (181).[632] The following complexes were used as catalysts for the reaction: $[PtCl_2(PBu_3)_2]$, $[RuH(Br)CO(PEt_2Ph)_3]$ (**137**), $[RuH(Cl)(Et_2PC_2H_4PEt_2)_2]$ (**138**), $[IrCl_3(PEt_2Ph)_3]$, $[IrCl_3(PBu_3)_3]$ and $[Ir(H)_2Cl(PPh_3)_3]$ (**139**). They underwent conversion to carbonyl complexes during the reaction, but no free carbon monoxide was detected. The reaction serves as a source of reducing power by virtue of the production of hydrogen and the addition of *n*-butyraldehyde led to its conversion to *n*-butanol. Both alkenes and alkynes have been reduced to alkanes by formic acid or formate ion. Ruthenium, rhodium, iridium and platinum complexes were used as catalysts, with $[RuCl_2(PPh_3)_4]$, $[RhCl(PPh_3)_3]$ (**23**) and $[IrH(CO)_2(PPh_3)_2]$ apparently being the most active.[633] These reactions required raised temperatures. $[RuH(Cl)(PPh_3)_3]$ (**3**) was shown to catalyze alkene reduction at room temperature in polar solvents.[634] $[RuH(OAc)(PPh_3)_3]$ (**7**) and $[RuCl_2(PPh_3)_3]$ (**2**) were somewhat less active.

$$HCO_2H \rightarrow H_2 + CO_2 \qquad (181)$$



(**137**)

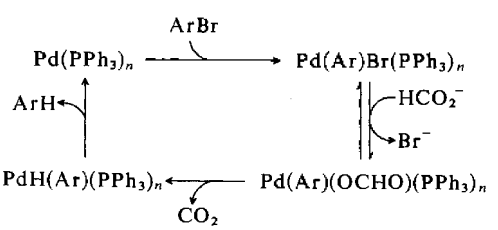


(**138**)

In the reduction of ketones to alcohols and β-ketoesters to hydroxyesters by formic acid, the complexes (**2**), (**3**), $[RuH(Cl)CO(PPh_3)_3]$ (**11**) and $[Ru(H)_2(PPh_3)_4]$ (**6**) were investigated as catalysts. Complex (**2**) was the most effective.[635,636]

The formate ion has been used for the dehalogenation of aryl bromides (equation 182).[637] Complexes studied as catalysts were (**2**), (**23**), $[RhCl(CO)(PPh_3)_2]$ (**71**), $[IrCl(CO)(PPh_3)_2]$ (**43**), $[Pd(PPh_3)_4]$ (**103**) and $[PdCl_2(PPh_3)_2]$ (**102**). Complex (**102**) exhibited the highest activity, but had to be used in presence of a large excess of PPh_3 to prevent precipitation of palladium metal. Initial reduction to palladium(0) complexes $[Pd(PPh_3)_n]$ occurred. The reactions were carried out in a two-phase system. Scheme 69 gives the predicted mechanism of the reaction.

$$ArBr + HCO_2^- \rightarrow ArH + CO_2 + Br^- \qquad (182)$$



Scheme 69

61.2.9.2 Acetaldehyde

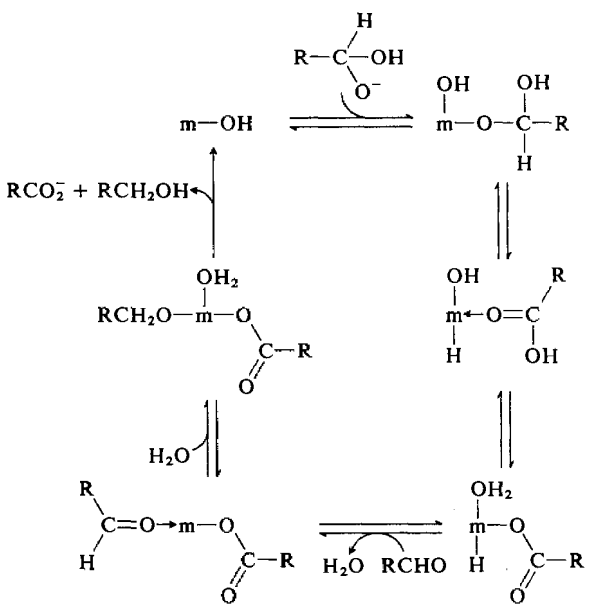
When pure acetaldehyde is treated with a catalytic amount of complex (**6**) at room temperature, a rapid reaction occurs giving ethyl acetate as product (equation 183).[639,640] The reaction occurs

with both aliphatic and aromatic aldehydes, but is inhibited if traces of carboxylic acids are present. In addition to complex (**6**), the reaction was also catalyzed by the complexes $[Ru(H)_2(PPh_3)_3]$, $[Ru(H)_2CO(PPh_3)_3]$, $[RuH(Cl)(PPh_3)_3]$, $[RuH(Cl)CO(PPh_3)_3]$, $[Ru(C_2H_4)(PPh_3)_3]$ and $[RuH(CH{=}CMeCOOEt)(PPh_3)_3]$. The complexes $[RuCl_2(PPh_3)_3]$ and $[Ru(CO)_3(PPh_3)_2]$ were inactive. Complexes of other metals showed little or no ability to catalyze the reaction. Two possibilities were considered regarding the mechanism of the reaction. One involves oxidative addition of the aldehyde C—H bond to a ruthenium(0) complex followed by insertion of aldehyde into the resulting hydride complex to give $[Ru(COR)OCH_2R(PPh_3)_3]$, which reductively eliminates the ester. The other involves a hydridoalkoxyruthenium(II) complex which inserts aldehyde into the Ru—O bond to give the intermediate $[RuH(OCHROCH_2R)(PPh_3)_3]$, which with a further mole of aldehyde eliminates ester and reforms the hydridoalkoxyruthenium(II) complex. In this second possible mechanism the ruthenium carries a 'redundant' hydride ligand throughout the catalytic cycle.

$$2MeCHO \rightarrow MeCO_2Et \tag{183}$$

When complexes such as $[Rh_2(C_5Me_5)_2(OH)_3]^+$, $[M_2(C_5Me_5)_2Cl_4]$ (M = Rh, Ir), $[Ru_2(p\text{-cymene})_2Cl_4]$ and $[Ru_2(C_6Me_6)_2(OH)_3]^+$ are used as catalyst, acetaldehyde disproportionates in the presence of water to give ethanol and acetic acid (equation 184).[640,641] Aldehyde hydrates were believed to be involved in the reaction. A number of points regarding the mechanism are still unclear, but the proposed steps are given in simplified form in Scheme 70.

$$2MeCHO + H_2O \rightarrow EtOH + MeCO_2H \tag{184}$$



(m = Rh(C_5Me_5), Ir(C_5Me_5) or Ru(arene))

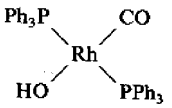
Scheme 70

Reaction (184) is considerably accelerated by the presence of a stoichiometric quantity of base and may thus be regarded as a metal-catalyzed Cannizzaro reaction. The metal-catalyzed reaction is far faster than that catalyzed by base alone.[641,642]

61.2.9.3 Acetonitrile

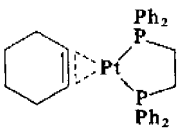
Nitriles can be catalytically hydrated, principally by palladium complexes (equation 185). In an initial study, $[Rh(OH)(CO)(PPh_3)_2]$ (**140**) was found to be the best catalyst.[643] Other complexes exhibiting catalytic activity were the iridium analogue of complex (**140**), $[Pt(C_6H_8)(diphos)]$ (**141**) and $[Pt(C_6H_8)(PPh_3)_2]$ (**142**).

$$MeCN + H_2O \rightarrow MeCONH_2 \tag{185}$$

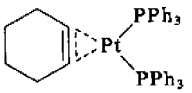


(**140**)

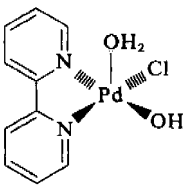
$[PdCl_2(bipy)]$ gave acetamide in good yield and with 100% selectivity when used as catalyst in basic solution.[644] A complex having the composition $[PdCl(OH)bipy(H_2O)]$ (**143**) was isolated and shown to be an effective catalyst for reaction (185).



(**141**)

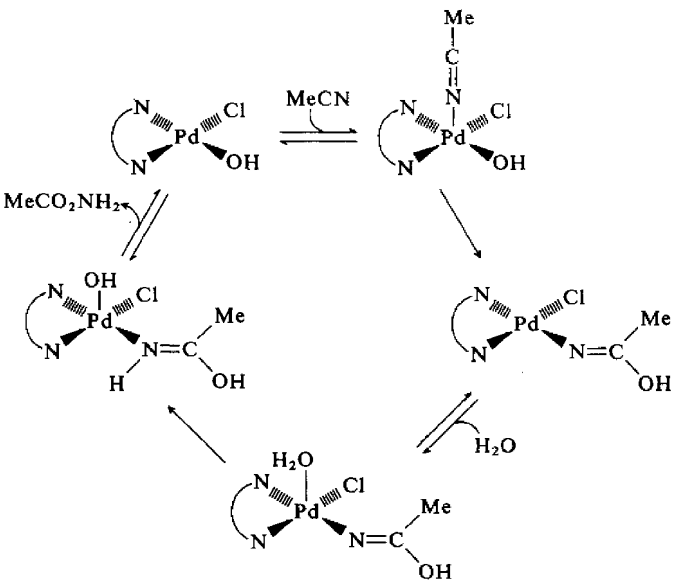


(**142**)



(**143**)

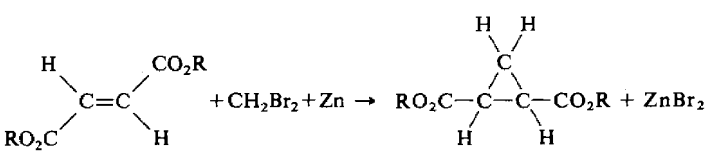
Other complexes of this type which were also active are $[PdCl(OH)phen(H_2O)]$ and $[PdX(OH)bipy(H_2O)]$ (X = Br, OAc, OH). Following a kinetic study using complex (**143**) as catalyst, the mechanism shown in Scheme 71 was formulated.[645] The complex first dissociates the water molecule to enter the catalytic cycle.



Scheme 71

61.2.9.4 Dihalomethanes

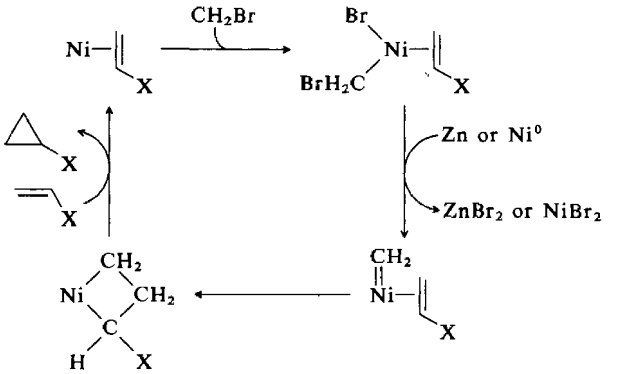
Dibromomethane reacts with activated alkenes in the presence of a halide acceptor and cobalt or nickel catalysts to give cyclopropane derivatives (equation 186).[646]



(186)

By using asymmetric alcohol residues in the ester, chirality could be induced at the ring carbon atoms. $CoCl_2$ and $NiBr_2$ were used as catalysts, in presence of NaI. The nickel-catalyzed reaction has been studied in more detail.[647] Zinc was again used as halide acceptor, together with $ZnBr_2$ or NaI. Electron-rich alkenes did not react. The nickel complexes employed were $[Ni(PPh_3)_4]$, $[Ni(cod)_2]$ and $[NiBr_2(PPh_3)_2]$ in addition to $NiBr_2$. It was generally necessary to choose the complex according to the alkene used. In some cases, PPh_3 inhibited the reaction. The nickel(II)

complexes were reduced by zinc to give nickel(0)-alkene species. The mechanism appears to involve a metallocycle as an intermediate (Scheme 72).



Scheme 72

In the absence of a halide acceptor, dichloromethane undergoes a simple addition to terminal alkenes (equation 187).[648] $[NiCl_2(PPh_3)_2]$ gave best results as catalyst, but $[RuCl_2(PPh_3)_3]$ (**2**) and $[PdCl_2(PPh_3)_2]$ were also active. High temperature is required. Other complexes of nickel, rhodium and cobalt were investigated, but only the former were catalytically active. Activated alkenes were not studied. The mechanism has not been investigated in detail, but on the basis of an observed inhibition of the reaction by 4-*t*-butylcatechol, the radical mechanism depicted in Scheme 73 was suggested.

$$CH_2Cl_2 + CH_2{=}CHR \rightarrow ClCH_2CH_2CHClR \quad (187)$$

$$Ni + CH_2Cl_2 \rightarrow Ni{-}Cl + \cdot CH_2Cl \quad (188)$$

$$\cdot CH_2Cl + CH_2{=}CHR \rightarrow ClCH_2CH_2\dot{C}HR \quad (189)$$

$$ClCH_2CH_2\dot{C}HR + Ni{-}Cl \rightarrow ClCH_2CH_2CHClR + Ni \quad (190)$$

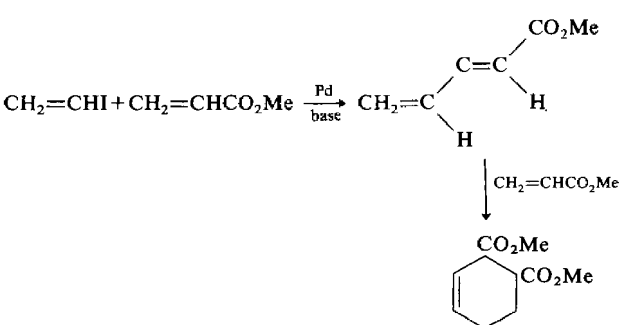
Scheme 73

61.2.9.5 Vinyl Halides

Analogous to the palladium-catalyzed arylation of alkenes with aryl halides (Section 61.2.8.4), vinyl halides can be used to prepare dienes according to equation (191).[649] A base is again needed in stoichiometric quantities. It should be noted that the dienes can be isolated as such only in certain cases. When vinyl iodide itself was used, only Diels-Alder products were obtained (Scheme 74).

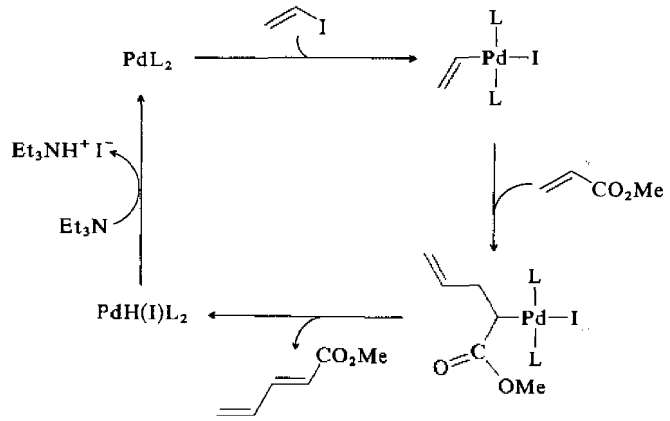
$$RCH{=}CHX + CH_2{=}CHCO_2Me + Et_3N \rightarrow RCH{=}CHCH{=}CHCO_2Me + Et_3NH^+ X^- \quad (191)$$

(R = H, alkyl)



Scheme 74

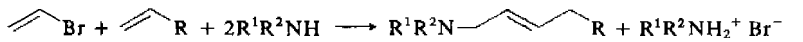
$[Pd(OAc)_2(PPh_3)_2]$ was generally used as catalyst precursor and is first reduced to palladium(0) after the manner of equation (179; X = OAc). The mechanism is believed to be as shown in Scheme 75.



Scheme 75

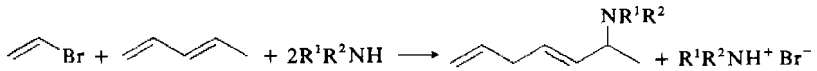
The configuration of the vinylic double bond is generally retained when substituted vinyl halides are used. With ethylene as the alkene component, terminal alkenes can be obtained.

If in the reactions of vinyl halides with alkenes a sterically unhindered secondary amine is used as base, different products are obtained (equation 192).[650] Incorporation of the amine occurs to give unsaturated tertiary amine as the major product. The conjugated dienes which would be expected from reaction (191) are present as minor products.



(192)

Morpholine, piperidine and diethylamine were used as bases. The catalyst precursor was $[Pd(OAc)_2]$ (**106**) and P(*o*-tol)$_3$ or a similar phosphine. The mechanism is thought to involve vinylation of the alkene as in Scheme 74 as the initial process. This leads to the formation of an η^3-allylpalladium derivative, which is then 'trapped' by the amine to give the final product. If dienes are used instead of monoenes, 2,5-dienylamines are produced (equation 193).[651]



(193)

61.2.9.6 Allene

In the presence of $[Pd(PPh_3)_4]$ (**103**) as catalyst, allene undergoes hydrosilylation (equation 194).[620] If the reaction is allowed to continue in the presence of excess of the silane, 1,3-bis(trichlorosilyl)propane is obtained.

$$H_2C{=}C{=}CH_2 + SiHCl_3 \rightarrow H_2C{=}CHCH_2SiCl_3 \qquad (194)$$

61.2.10 REFERENCES

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61.3

Metal Complexes in Oxidation

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61.3.1 GENERAL CONSIDERATIONS

61.3.1.1 Introduction

Oxygen, in its free and combined states, constitutes 46.6% of the mass of the Earth's crust, making it the most abundant element. Combining molecular oxygen with hydrocarbons is a rewarding goal, in that it provides a direct synthesis of valuable oxygenated products such as alcohols, ketones, epoxides, glycols, carboxylic acids and esters, phenols, *etc.* Millions of tons of oxygen compounds are now produced annually by this method (see Table 2). However, this reaction involves two main difficulties.

(i) Dioxygen has a triplet ground state, and its direct combination with singlet organic molecules is a spin-forbidden process. This, however, allows living organisms to exist in an oxygen atmosphere. Though thermodynamically favored, the addition of dioxygen to hydrocarbons generally requires high activation energies for the initiation step, but once underway is difficult to control.

(ii) The primary oxygenated products (*e.g.* alcohols, ketones, epoxides) are often more oxidizable than the initial hydrocarbons. This results in operating at low conversions to obtain acceptable product selectivities, and large-scale and expensive recycling of the starting material is often required.

Dioxygen plays a central role in living cells. It can either be transported by respiratory pigments and released at active sites, or activated in enzymatic systems called oxygenases. At physiological temperature these oxygenases bring about a great number of selective oxidations such as hydroxylation of hydrocarbons, epoxidation of alkenes, oxidative cleavage, *etc.* A common feature of all these oxygen-carrying and activating systems lies in the fact that transition metals are mostly involved as the active center.[1] Transition metals having multiple spin and oxidation states can readily interact with dioxygen, even to the extent of forming isolatable oxygen adducts.[2–13] In these associations the metal acts as a reducing agent and can also polarize the dioxygen bond, facilitating its cleavage. It can also simultaneously bind dioxygen and the substrate, and then create the favorable entropic conditions for a selective oxidation to occur.

Owing to space limitations, only the most representative examples of oxidations mediated by transition metal complexes will be considered in this chapter. Special emphasis will be placed on oxygen transfer reactions occurring in the coordination sphere of the metal, and both stoichiometric

and catalytic transformatins will be envisaged. Oxygen sources may be molecular oxygen itself, peroxides such as hydrogen peroxide or alkyl hydroperoxides, or other reagents such as alkaline hypohalites or iodosylbenzene. The substrates that will be particularly studied are hydrocarbons of petroleum origin such as alkenes, alkanes or arenes. A classification of oxidation reactions according to the nature of the actual oxygen source has been preferred, although many oxygen transfer reactions have not yet been assigned any definite mechanism. Another difficulty with this classification lies in the fact that the original oxygenated complex can be transformed into other reactive species. The general aim of this chapter is to attempt to make a balanced description and rationalization of oxygen transfer reactions. For more detailed information the reader is referred to the literature in this field, which will be cited throughout this chapter.

61.3.1.2 Metal–Oxygen Species

The different oxygenated species (**1**)-(**8**) which are liable to play a role in oxidation processes are schematically represented in Figure 1. Dioxygen is a potential four-electron acceptor, and its interaction with reduced transition metals is expected to be complex.[14]

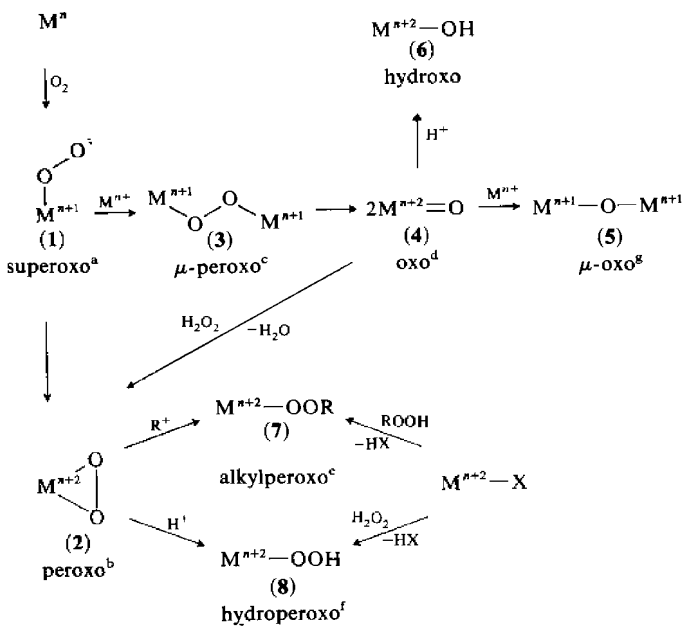


Figure 1. Metal–oxygen species: [a] Fe^{III}, Co^{III}; [b] Ti^{IV}, V^{V}, Nb^{V}, Ta^{V}, Cr^{VI}, Mo^{VI}, W^{VI}, $Ru^{II;IV}$, $Os^{II,IV}$, Co^{III}, Rh^{III}, Ir^{III}, Ni^{II}, Pd^{II}, Pt^{II}, U^{VI}, Th^{IV}; [c] Co^{III}, Rh^{III}, Pd^{II}, Pt^{II}, U^{VI}, La^{III}; [d] Ti^{IV}, Zr^{IV}, $V^{IV,V}$, Nb^{V}, Cr^{IV-VI}, Mo^{IV-VI}, W^{IV-VI}, Mn^{VII}, Re^{VII}, $Ru^{VI,VIII}$, $Os^{IV-VIII}$; [e] V^{V}, Co^{III}, Rh^{III}, Ir^{III}, Pd^{II}, $Pt^{II,IV}$; [f] Mo^{VI}, Co^{III}, Rh^{III}, Pt^{II}, Cu^{II}; and [g] Ti^{IV}, Zr^{IV}, V^{V}, Nb^{V}, Ta^{V}, Mo^{VI}, W^{VI}, Mn^{III}, Fe^{III}

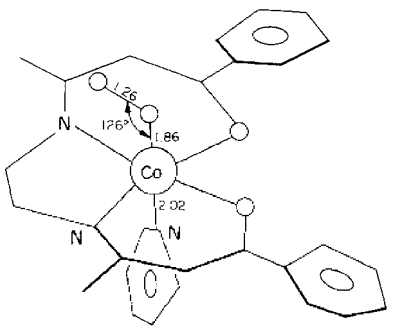
The first step consists of the formation of the dioxygen adduct which can have either a superoxo structure (**1**) if the metal is a potential one-electron donor, or a peroxo structure (**2**) if the metal is a potential two-electron donor. These superoxo or peroxo complexes can be considered as the formal, but not chemical, analogs of the superoxide O_2^- and peroxide O_2^{2-} anions. The superoxo complex (**1**) can further react with a second reduced metal atom to give the μ-peroxo species (**3**), which can cleave itself into the oxo species (**4**), which may be hydrolyzed to give the hydroxo species (**6**) or react with a second metal atom to give the μ-oxo species (**5**). The alkylperoxo (**7**) and hydroperoxo (**8**) species can result from the alkylation or protonation of the peroxo species (**2**), or from anion exchange from metal salts by alkyl hydroperoxides or hydrogen peroxide.

The existence and stability of the oxygenated forms (**1**)-(**8**) depend on the nature of the metal and of the ligands attached to it. The metals for which well-characterized oxygenated species have been synthesized are listed in Figure 1.

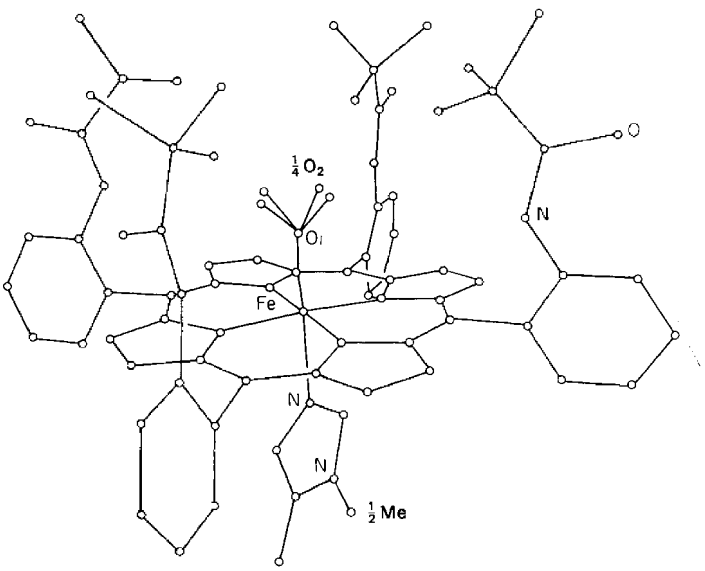
61.3.1.2.1 Superoxo complexes

Superoxo complexes have been characterized by X-ray structural analysis for iron and cobalt only. Dioxygen coordination occurs through a bent 'end-on' mode, with an O—O length ranging

from 1.15 to 1.26 Å, an M—O—O angle of between 115 and 137°, and a characteristic infrared ν(0—0) vibration at 1100-1200 cm^{-1}.[10] Two representative examples are the paramagnetic cobalt Schiff base complex Co(Bzacen)pyO_2 (**9**; Bzacen = *N,N'*-ethylenebis(benzoylacetoneiminato)[15] and the diamagnetic iron 'picket-fence' porphyrin Fe(TpivPP)(Meim)O_2 (**10**) where the iron atom is surrounded by a cage which prevents the dioxygen species from reacting with another iron atom (TpivPP = *meso*-tetrakis($\alpha,\alpha,\alpha,\alpha$-*o*-pivalamidophenyl)porphyrinato, Meim = 1-methylimidazole).[16]



(9)



(10)

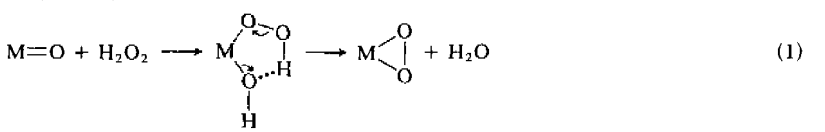
These superoxo complexes are relevant models for the naturally occurring oxygen carriers hemoglobin and myoglobin, which contain ferroprotoporphyrin IX as an active center in which the sixth axial postion is occupied by the imidazole moiety of histidine.[17] They also intervene as primary oxygen adducts in enzymatic cytochrome *P*-450 oxygenases.[18]

61.3.1.2.2 Peroxo complexes[19,20]

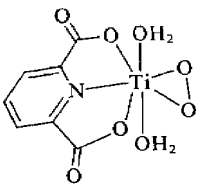
Peroxo complexes are far more numerous than superoxo complexes and have been well characterized for early d^0 transition metals (Ti^{IV}, V^V, Nb^V, Ta^V, Cr^{VI}, Mo^{VI}, W^{VI}) and Group VIII d^4 (Ru^{IV}), d^6 (Ru^{II}, Os^{II}, Co^{III}, Rh^{III}, Ir^{III}) and d^8 (Ni^{II}, Pd^{II}, Pt^{II}) complexes. With some exceptions [*e.g.* $Cr^{IV}(NH_3)_3(O_2)_2$], they are mostly diamagnetic. In the majority of these 'side-on' dioxygen complexes the peroxo triangle is not isosceles, one M—O bond being somewhat shorter than the other. The triangular peroxo group is characterized for all the metals by a peroxide O—O distance of between 1.4 and 1.5 Å and three infrared vibrations of the C_{2v} structure at 800-950 cm^{-1} [ν(O—O)] and 500-650 cm^{-1} [ν(M—O), sym and asym]. The bipyramidal pentagonal structure is most frequently found for early transition metals, while the trigonal bipyramidal and trigonal structures often exist for Group VIII metal complexes.

Peroxo-metal complexes can be synthesized by two main methods.

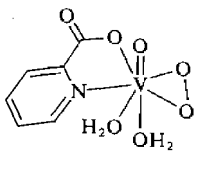
(a) For early transition metals, from the reaction of hydrogen peroxide with high-valent metal-oxo complexes, *via* the formation of an oxo-hydroperoxo intermediate (equation 1). In this case, dioxygen is already reduced and is in the peroxide form, and the d^0 metal in its higher oxidation state does not possess any electrons to be given to dioxygen by back-bonding. For the majority of these complexes there is little variation in O—O bond lengths despite the difference in metal, ligands, valence state and structure. Some examples of peroxo complexes of titanium, vanadium, niobium, chromium and molybdenum are shown in (**11-15**).



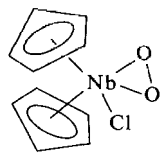
(1)



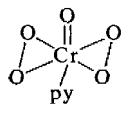
(**11**)[21]



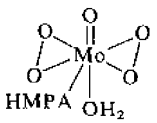
(**12**)[22]



(**13**)[23]



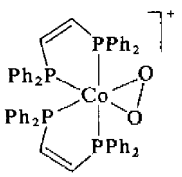
(**14**)[24]



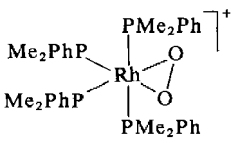
(**15**)[25]

(b) For Group VIII metals, from the direct interaction of dioxygen with the reduced two-electron donor metal complex (equation 2). The bonding between the metal and dioxygen is similar to that of the Dewar-Chatt model for metal-alkene complexes,[26] with predominant π-bonding from the filled *d*-orbitals of the metal to the antibonding $1\pi g$ orbital of dioxygen. Higher electron density at the metal favors the bonding of dioxygen and its reduction to a peroxide form (**16–21**). In the well-known series of Vaska's dioxygen complexes $IrL_2(CO)X(O_2)$, the binding of O_2 becomes more irreversible and the O—O distance increases as the auxiliary ligands become less electronegative ($L = PPh_3 > PPh_2Et$; $X = Cl > Br > I$).[27]

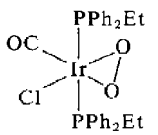
$$M^n + O_2 \longrightarrow M^{n+2}\!\!\begin{array}{l}O\\O\end{array} \qquad (2)$$



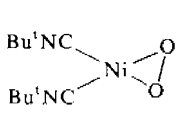
(**16**)[28]



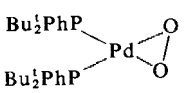
(**17**)[29]



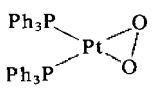
(**18**)[30]



(**19**)[31]



(**20**)[32]



(**21**)[33]

Despite the different mode of preparation and the greater influence of the metal environment in the case of Group VIII dioxygen adducts than in the case of early d^0 metal-peroxo complexes, no distinction can be made between these two types of dioxygen complex. In fact, several peroxo complexes can be obtained from both oxygen sources (equations 3[34] and 4[35,36]).

$$[Co^{I}(tetars)]^+ + O_2 \rightarrow [Co^{III}(O_2)(tetars)]^+ \leftarrow [Co^{III}(H_2O)_2(tetars)]^{3+} + H_2O_2 \qquad (3)$$

tetars = $[Me_2As(CH_2)_3As(Ph)CH_2]_2$

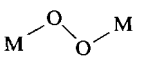
$$(TPP)Ti^{IV}{=}O \xrightarrow[-H_2O]{H_2O_2} (TPP)Ti\!\!\begin{array}{l}O\\O\end{array} \xleftarrow{-(TPP)TiF_2} 2(TPP)Ti^{III}F + O_2 \qquad (4)$$

TPP = *meso*-tetraphenylporphyrin

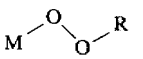
Peroxo-metal complexes are extremely important reactive intermediates in catalytic oxidations involving molecular oxygen or hydrogen peroxide as the oxygen source.

61.3.1.2.3 μ-Peroxo complexes

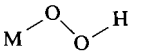
In complexes (**3**), (**7**) and (**8**), dioxygen can be inserted between two metal atoms (bimetallic μ-peroxo complexes), between one metal and one carbon atom (alkylperoxo complexes) or between one metal and one hydrogen atom (hydroperoxo complexes).



(3)



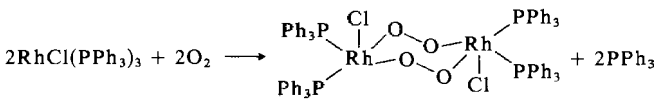
(7)



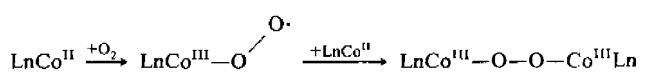
(8)

(i) Bimetallic μ-peroxo complexes (**3**)

The complexes can be obtained from the reaction of a Rh^{I} complex with O_2 (equation 5),[37] from the reaction of a Co^{III}-superoxo complex with a reduced metal (equation 6),[38] from the acid hydrolysis of a platinum-peroxo complex[39] (equation 7) or from the reaction of potassium superoxide with rhodium (equation 8)[40] or palladium complexes.[41]

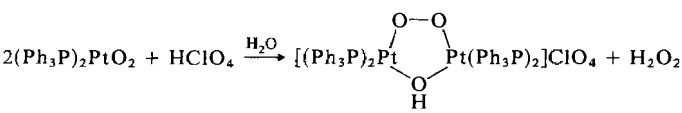


(5)

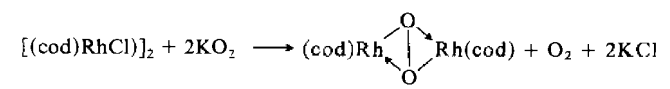


Ln = CN, NH_3, salen, *etc.*

(6)



(7)

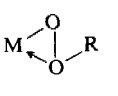


(8)

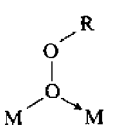
These complexes resemble peroxides, with an O—O distance of between 1.4 and 1.5 Å.

(ii) Alkylperoxo complexes (**7**)

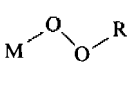
These complexes can exist in a triangular peroxo form (**7a**) for early d^0 transition metals, or in a bridged (**7b**) or linear (**7c**) form for Group VIII metals. They can be obtained from the reaction of alkyl hydroperoxides with transition metal complexes (equations 9 and 10),[42,46] from the insertion of O_2 into a cobalt-carbon bond (equation 11),[43] from the alkylation of a platinum-peroxo complex (equation 12),[44] or from the reaction of a cobalt-superoxo complex with a substituted phenol (equation 13).[45] Some well-characterized alkylperoxo complexes are shown (**22–24**).



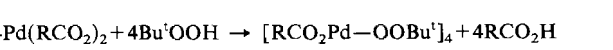
(7a)



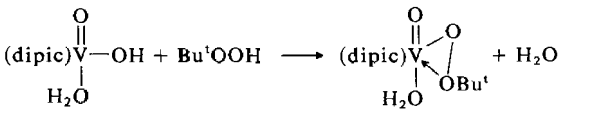
(7b)



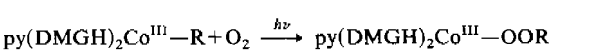
(7c)



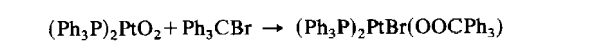
(9)



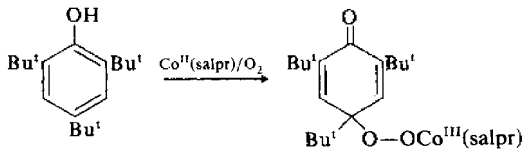
(10)



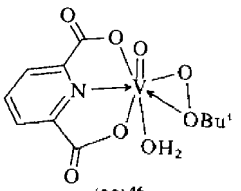
(11)



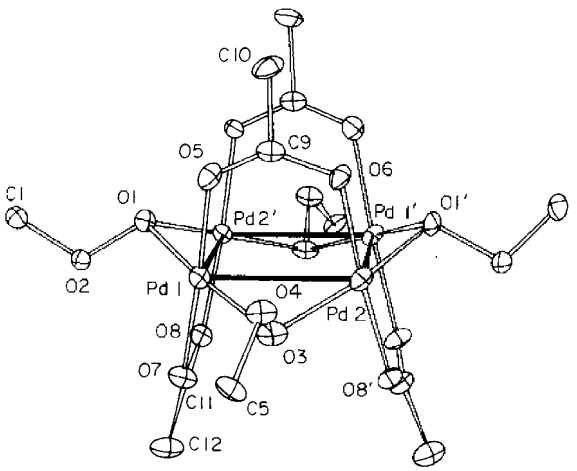
(12)



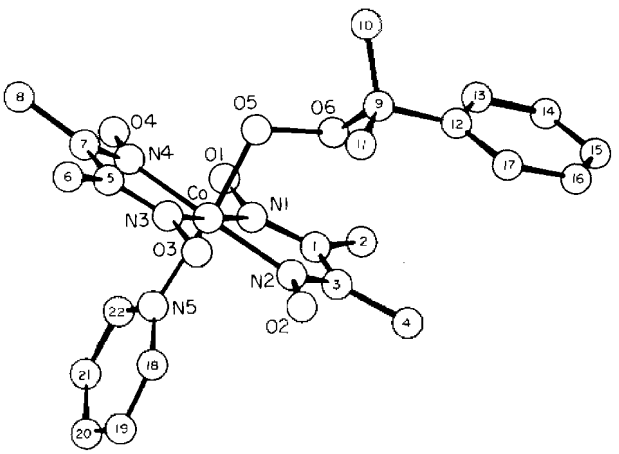
(13)



(22)[46]



(23)[42]



(24)[43]

Alkylperoxo species are extremely important reactive intermediates in the metal-catalyzed oxidation of hydrocarbons by alkyl hydroperoxides.

(iii) Hydroperoxo complexes (8)

Very few of these compounds have been characterized by X-ray crystallographic methods. As with alkylperoxo complexes, they can have a linear or a bridged structure, but no triangular form

is known. They can be prepared from the reaction of H_2O_2 with a metal salt (equation 14),[47] from the insertion of O_2 into a metal hydride bond (equation 15),[48] or from the hydrolysis of a metal-peroxo complex (equation 16).[49]

$$L_2Pt(CF_3)OH + H_2O_2 \rightarrow L_2Pt(CF_3)OOH + H_2O \quad (14)$$

$$[CoH(CN)_5]^{3-} + O_2 \rightarrow [Co(OOH)(CN)_5]^{3-} \quad (15)$$

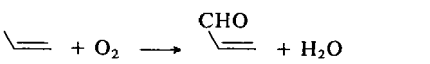
$$(Ph_3P)_2PtO_2 + CF_3CO_2H \rightarrow (Ph_3P)_2Pt(CF_3CO_2)OOH \quad (16)$$

Hydroperoxo species intervene as reactive species in the Group VIII metal-catalyzed oxidation of alkenes by O_2 or H_2O_2.

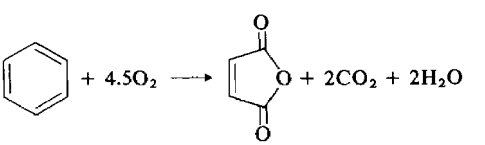
61.3.1.2.4 Oxo complexes (4)

Oxo-metal (M=O) complexes have been effectively characterized for the early transition elements.[50-52] Group VIIb and VIII metals also give stable oxo compounds such as MnO_4^-, ReO_4^-, RuO_4 and OsO_4 in which the metal is in its higher oxidation state. Such compounds are well known to organic chemists as stoichiometric hydrocarbon-oxidizing reagents.

Oxo-metal complexes also intervene as active species in the heterogeneous gas-phase oxidation of hydrocarbons over metal oxide or mixed metal oxide catalysts at high temperatures. Characteristic examples are the bismuth molybdate-catalyzed oxidation of propene to acrolein and the V_2O_5-catalyzed oxidation of benzene to maleic anhydride (equations 17 and 18).[53]



(17)



(18)

$Fe^{V}=O$ and $Mn^{V}=O$ have also recently emerged as plausible reactive intermediates in the oxidation of hydrocarbons by iodosylbenzene, amine *N*-oxide, percarboxylic acids, hypochlorites, *etc.* catalyzed by iron or manganese porphyrins. Current opinion favors $Fe^{V}=O$ species as the active oxidant in cytochrome *P*-450 monooxygenases.[54,55]

61.3.1.3 Homolytic and Heterolytic Oxidations

As rationalized by Sheldon and Kochi,[56] metal-catalyzed oxidations may be conveniently divided into two types, designated as homolytic and heterolytic. The main characteristics of homolytic and heterolytic oxidations are schematically summarized in Table 1.

Homolytic oxidations involve free radical intermediates and are catalyzed by first-row transition metals characterized by one-electron oxidation-reduction steps, *e.g.* Co^{III}/Co^{II}, Mn^{III}/Mn^{II}. The hydrocarbon substrate is generally not coordinated to the metal and is oxidized outside the coordination sphere. Consequently, the oxidation is not very selective and does not often preserve the stereochemical configuration of the substrate.

Heterolytic oxidations generally require activation of the substrate by coordination to the metal and are generally highly selective and steroespecific. They do not involve free radical intermediates and use second- and third-row transition metals which conserve their oxidation state or change it by a two-electron oxidation-reduction step.

However, although convenient, this classification is not rigorous and there are a number of borderline examples and exceptions. For example, many enzymic oxygenases containing first-row metals (*e.g.* Fe, Cu) as active centers and homolytic in nature act with a very high regio- and stereo-selectivity. In this case the role of the protein cage around the active center is essential for the substrate-enzyme association and the right orientation of the substrate toward the active

Table 1 The Main Characteristics of Homolytic and Heterolytic Oxidations

Homolytic oxidations	*Heterolytic oxidations*
Characteristics	
Free-radical intermediates	No free-radical intermediates
Outer-sphere oxidations in bimolecular steps. The substrate is generally not coordinated	The reaction occurs in the coordination sphere of the metal. The substrate is generally activated by coordination.
Oxidations generally not very selective and not stereospecific	High selectivity and stereospecificity of the transformation
One-electron oxidation and reduction step of the metal	No change in the oxidation state of the metal or two-electron steps
Transition metals commonly involved	
V^{V}/V^{IV}, Cr^{VI}/Cr^{V}, Mn^{III}/Mn^{II}, Fe^{III}/Fe^{II}, Co^{III}/Co^{II}, Cu^{II}/Cu^{I}	Ti^{V}, V^{V}, Cr^{VI}, Mo^{VI}, W^{VI}, Mn^{VII}, Ru^{VII}, $Os^{VI-VIII}$, Rh^{III}/Rh^{I}, Ir^{III}/Ir^{I}, Pd^{II}/Pd^{0}, Pt^{II}/Pt^{0}
Relevant oxidations	
Nonstereoselective epoxidation of alkenes (V, Mn, Fe)	Stereoselective epoxidation of alkenes (Ti, V, Mo, W)
Hydroxylation of alkanes and arenes (V, Cr, Mn, Fe, Co, Cu)	Ketonization of alkenes (Rh, Ir, Pd, Pt)

center. In other cases the free radical carbon intermediates can keep close to the metal and react in a concerted way before inversion.

There are also several situations where the metal can act as both a homolytic and heterolytic catalyst. For example, vanadium complexes catalyze the epoxidation of allylic alcohols by alkyl hydroperoxides stereoselectively,[57] and they involve vanadium(V) alkyl peroxides as reactive intermediates. However, vanadium(V)-alkyl peroxide complexes such as (dipic)VO(OOR)L, having no available coordination site for the complexation of alkenes to occur, react homolytically.[46] On the other hand, Group VIII dioxygen complexes generally oxidize alkenes homolytically under forced conditions, while some rhodium–dioxygen complexes oxidize terminal alkenes to methyl ketones at room temperature.

The homolytic and heterolytic nature of the oxidation is principally governed by the nature of the metal, but also by the nature of the ligands, the availability of coordination sites, the nature of the substrate and the temperature conditions. Consequently, the chemist has to overcome several difficulties, some inherent to homogeneous catalysis, some inherent to oxidation chemistry: (i) a good choice of ligands which resist the oxidation conditions, but such a choice is limited; (ii) a good choice of substrate, adapted to the metal used (for example, cyclohexene is a suitable substrate for d^0 metals, but unsuitable for Group VIII metals); and (iii) a good choice of solvent and reaction conditions. Transition metals very often catalyze the homolytic autoxidation of the substrate by molecular oxygen, and particular care is sometimes necessary to distinguish a heterolytic from a homolytic oxidation.

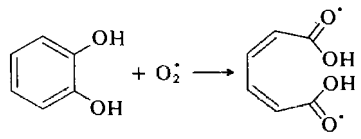
61.3.1.4 Biological Aspects

Enzymes that directly incorporate molecular oxygen into organic substrates play a crucial role in many fundamental biological processes such as degradation of natural products in the biosphere, biosynthesis and metabolism of amino acids, hormones, drugs, *etc.* A wide variety of enzymic oxygenases has been identified and isolated from microorganisms, plants and animals. A detailed description of these enzymes is beyond the scope of this chapter, but several books and review articles are available.[1,58–62]

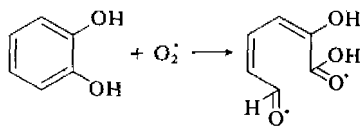
The main relevant characteristic properties of oxygenases are that they mostly involve transition metals (particularly iron and copper) as active centers and that they activate dioxygen and transfer it selectively to organic substrates. Oxygenases can be conveniently classified into two main families.

(1) *Dioxygenases* catalyze the incorporation of both atoms of molecular oxygen into the substrate. Microbial *pyrocatechol dioxygenases* contain non-heme iron as the sole cofactor and catalyze the oxidative cleavage of pyrocatechol to *cis,cis*-muconic acid (intradiol; equation 19) or to α-hydroxymuconic ε-semialdehyde (extradiol; equation 20).[63–65] On

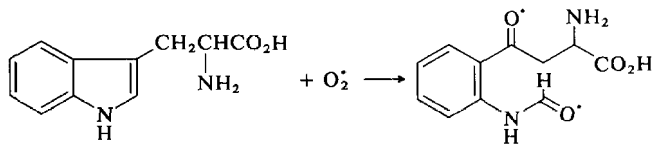
the other hand, *tryptophan 2,3-dioxygenase* contains both ferriprotoporphyrin IX and cuprous ion as the active site and catalyzes the oxidative cleavage of L-tryptophan to formylkynurenine (equation 21).[66]



(19)



(20)

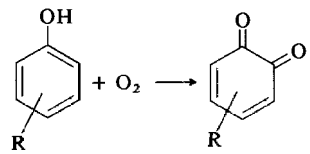


(21)

(2) *Monooxygenases* catalyze the incorporation of only one atom of molecular oxygen into the substrate, while the other one is reduced to water. In *internal monooxygenases* the hydrogen donor is the substrate itself (equation 22), while *external monooxygenases* require a hydrogen donor cosubstrate DH_2 (equation 23) such as $NADPH_2$ (reduced nicotinamide adenine dinucleotide phosphate) or $NADH_2$ (reduced nicotinamide adenine dinucleotide). Tyrosinase is one example of an internal monooxygenase; it contains copper as the active metal and transforms phenols into *o*-quinones (equation 24).[67,68] External monooxygenases containing cytochrome *P*-450 as an active center have been extensively studied in recent years.[69-73] Cytochrome *P*-450 molecules comprise hemoproteins containing ferriprotoporphyrin IX bonded to a polypeptide chain by a cysteinate sulfide atom acting as a strongly donating axial ligand. They have been isolated from numerous bacteria, adrenal mitochondria and mammalian liver microsomes.

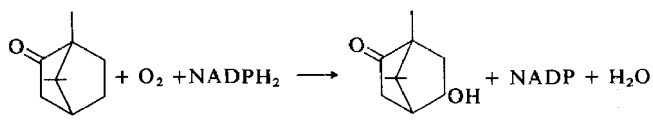
$$SH_2 + O_2 \rightarrow SO + H_2O \tag{22}$$

$$S + DH_2 + O_2 \rightarrow SO + D + H_2O \tag{23}$$



(24)

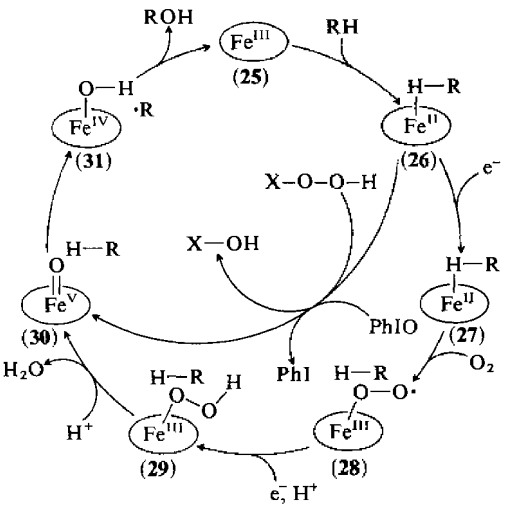
The camphor 5-oxygenase of *Pseudomonas putida*, which has been isolated in crystalline form, catalyzes the hydroxylation of camphor (equation 25).[69]



(25)

In mammalian liver microsomes, cytochrome *P*-450 is not specific and catalyzes a wide variety of oxidative transformations, such as: (i) aliphatic C—H hydroxylation occurring at the most nucleophilic C—H bonds (tertiary > secondary > primary); (ii) aromatic hydroxylation at the most nucleophilic positions with a characteristic intramolecular migration and retention of substituents of the aromatic ring, called an NIH shift,[74] which indicates the intermediate formation of arene oxides; (iii) epoxidation of alkenes; and (iv) dealkylation (O, N, S) or oxidation (N, S) of heteroatoms. In mammalian liver these processes are of considerable importance in the elimination of xenobiotics and the metabolism of drugs, and also in the transformation of innocuous molecules into toxic or carcinogenic substances.[75-77]

It is now generally understood that the mechanism of hydroxylation by cytochrome *P*-450 proceeds by two successive one-electron reduction steps of the heme center, transforming dioxygen into a peroxide species bonded to iron (Scheme 1).[73,78] Well-defined steps (**25**) → (**31**) involve: (a) the formation of a high-spin Fe^{III}-enzyme-substrate complex (**26**); (b) one-electron reduction of (**26**) to a high-spin ferrocytochrome (**27**); (c) addition of dioxygen to form a superoxo-Fe^{III} complex (**28**); and (d) one-electron reduction of the superoxo complex to a peroxide complex (**29**).



Scheme 1

The mechanism of oxygen transfer from the peroxide (**29**) to the substrate still remains a matter of controversy. Current opinions favor the formation of a high-valent FeO^{3+} (or $Fe^{V}{=}O$ or $Fe^{IV}{-}O\cdot$) (**30**) active species, which acts as a homolytic hydrogen abstractor from the substrate.[78,79] An alternative mechanism considers the Fe^{III}-peroxide complex as the actual hydroxylating reagent,[12] by analogy with the reactivity of vanadium(V)-peroxo[22] and -alkylperoxo complexes[46] and that of chromium(VI)-peroxo complexes (see below).[80]

It is noteworthy that cytochrome *P*-450 can also function with peroxide oxygen sources other than O_2+2e^-, *viz.* iodosylbenzene,[81] alkyl hydroperoxides,[78] or percarboxylic acids.[82]

61.3.1.5 Industrial Aspects

Millions of tons of oxygenated compounds are annually produced in the world and find applications in all areas of the chemical industry.[83–94] Table 2 lists the main industrial oxygenated products obtained by catalytic oxidation, their capacities, their mode of manufacture and their applications. Most of these processes use dioxygen or air as the oxidant and operate under homogeneous or heterogeneous conditions.

The liquid-phase oxidation of hydrocarbons represents the largest scale application of homogeneous catalysis. Liquid-phase process technology enables better control of reaction conditions and conversions, and more convenient heat removal from these highly exothermic oxidations.

Homolytic liquid-phase processes are generally well suited to the synthesis of carboxylic acids, *viz.* acetic, benzoic or terephthalic acids which are resistant to further oxidation. These processes operate at high temperature (150–250 °C) and generally use soluble cobalt or manganese salts as the main catalyst components. High conversions and selectivities are usually obtained with methyl-substituted aromatic hydrocarbons such as toluene and xylenes.[95,96] The cobalt-catalyzed oxidation of cyclohexane by air to a cyclohexanol-cyclohexanone mixture is a very important industrial process since these products are intermediates in the manufacture of adipic acid (for nylon 6,6) and caprolactam (nylon 6). However, the conversion is limited to *ca.* 10% in order to prevent consecutive oxidations, with roughly 70% selectivity.[97]

Heterolytic liquid-phase oxidation processes are more recent than homolytic ones. The two major applications are the Wacker process for oxidation of ethylene to acetaldehyde by air, catalyzed by $PdCl_2$–$CuCl_2$ systems,[98] and the Arco oxirane[99] or Shell process[100] for epoxidation of propylene by *t*-butyl or ethylbenzene hydroperoxide catalyzed by molybdenum or titanium complexes. These heterolytic reactions require less drastic conditions than the homolytic ones

Table 2 Main Industrial Catalytic Oxidation Processes[a]

Product	*Substrate*	*Oxygen source*	*World capacities*[b] *($Mt\ y^{-1}$)*	*Reaction conditions*[c]	*Chemical characteristics*	*Process*	*Main applications*
Formaldehyde	Methanol	O_2	5	350 °C, 1 bar, [$Fe(MoO_4)_3$] C = 95%, S = 92%	Heterogeneous, heterolytic	Perstop-Reichhold, Hiaq-Lurgi, Lummus Montedison, SBA, IFP-CDF	Resins, polyols conservation
Acetaldehyde	Ethylene	O_2	3	100–130 °C, 3–10 bar, [$PdCl_2$–$CuCl_2$], C = 40%, S = 95%; one or two steps	Homogeneous, heterolytic	Wacker-Hoechst	Acetic acid, *n*-butanol 2-ethylhexanol
Acetic acid	Acetaldehyde or butane or naphthas	O_2	5	From MeCHO: 60 °C, [Co], S = 95%; from C_4 compounds: 190 °C, 60 bar, [Co], C = 30%, S = 45%	Homogeneous, homolytic	Hoechst, Rh-Poulenc (MeCHO), Celanese, Hulls (C_4's), Distillers, BP(naphthas)	Vinyl acetate, cellulose acetate, Ac_2O, solvent
Ethylene oxide	Ethylene	O_2	7.5	270 °C, 10–30 bar, [Ag], C = 20%, S = 65–75%	Heterogeneous, heterolytic	UCC, Shell, ICI, Scientific Design	Ethylene glycol, polyesters
Propene oxide	Propene	Bu^{t}OOH or PhCHMeOOH	3	130 °C, 45 bar, [Mo](ARCO) Ti/SiO_2(Shell) C = 15%, S = 92%	Homogeneous, heterolytic	ARCO (Mo), Shell (Ti)	Polyurethane, propylene glycol
Vinyl acetate	Ethylene + acetic acid	O_2	2.6	180 °C, 5–10 bar, [Pd/SiO_2] C = 15%, S = 90%	Heterogeneous, heterolytic	Bayer-Hoechst, USI	Polymers
Acrylic acid	Propene	O_2	1.3	$C_3^= \rightarrow$ acrolein: 350 °C, [$Bi_2O_3MoO_3]_n$, S = 80%; acrolein $\rightarrow$ acrylic acid: 250 °C, [Mo/V], S = 80%	Heterogeneous, heterolytic	UCC, Autochem, Shell, Sohio, Nippon, Shokubai	Polymers
Cyclohexanol + cyclohexanone	Cyclohexane	O_2	2	160 °C, 10 bar, [Co], C = 6–10%, S = 65–75%	Homogeneous, homolytic	Dupont, ICI, DSM, Scientific Design (boric acid)	Adipic acid (caprolactam)
Terephthalic acid	*p*-Xylene	O_2	8	200 °C, 15 bar, [$Co(OAc)_2 + Br^-$], AcOH, C = 95%, S = 90%	Homogeneous, homolytic	Amoco-Mid century, Teijin, Dynamit Nobel (dimethylterephthalate)	Polyesters
Benzoic acid	Toluene	O_2	0.5	120 °C, 3 bar [Co/Br], AcOH, C = 90%, S = 90%	Homogeneous, homolytic	Dow, Amoco	Phenol
Maleic anhydride	Benzene or butenes	O_2	0.6	400 °C, 3 bar [$V_2O_5/MoO_3/H_3PO_4$] C = 90%, S = 45–60%	Homogeneous, homolytic	Scientific Design (benzene) Petrotex (C_4)	Polymers, fine chemicals
Phthalic anhydride	Naphthalene or *o*-xylene	O_2	2	400 °C, 3 bar, [V/Mo], C = 90%, S = 75%	Heterogeneous, heterolytic	Chemisches Fabrik, Monsanto, Cyanamid, ICI, Rh-Poulenc	Plasticizers

[a] Data taken from refs. 83–94.
[b] Estimated values for 1981. These approximate values include production by other nonoxidative processes.
[c] C = conversion, S = selectivity.

and are much more selective. The chemistry of these processes will be described in detail in the following sections.

Heterogeneous oxidative processes operate at high temperatures (250–450 °C) and are useful for the synthesis of acrolein and acrylic acid from propylene over bismuth molybdate catalysts, the synthesis of maleic and phthalic anhydrides from the oxidation of benzene (or C_4 compounds) and naphthalene (or *o*-xylene) respectively over vanadium oxide,[101] and the synthesis of ethylene oxide from ethylene over silver catalysts.[102]

The recent dramatic increase in the price of petroleum feedstocks has made the search for high selectivities more urgent. Several new processes based on carbon monoxide sources are currently competing with older oxidation processes.[103,104] The more straightforward synthesis of acetic acid from methanol carbonylation (Monsanto process) has made the Wacker process obsolete for the manufacture of acetaldehyde, which used to be one of the main acetic acid precursors. Several new methods for the synthesis of ethylene glycol have also recently emerged and will compete with the epoxidation of ethylene, which is not sufficiently selective. The direct synthesis of ethylene

Table 3 Reactivity of Metal–Peroxo Complexes

Peroxo complexes[a]	*Structure*[b]	D(O—O) (Å)	ν(O—O) (cm^{-1})	*Oxygen Source*	*Reactivity*[c] *and/or refs.*
d° Metals					
$Ti(O_2)(pic)_2(HMPA)$ (**32**)	PB	1.42	895	H_2O_2	NR, PO, MF[106]
$Ti(O_2)(OEP)$ (**33**)	—	1.44	895	H_2O_2, O_2	NR[107]
$VO(O_2)(pic)(H_2O)_2$ (**12**)	PB	1.435	935	H_2O_2	NSE, HA, HB[22]
$[VO(O_2)(pic)_2]-H^+/HMPA$ (**34**)	—	—	940	H_2O_2	NSE, HA, HB[22]
$Nb(O_2)Cp_2Cl$ (**13**)	PT	1.47	870	H_2O_2	NR[23,108]
$[Nb(O_2)_2(pic)_2]PPh_4$ (**35**)	DH	—	850, 865	H_2O_2	NR[109]
$[Nb(O_2)_2(C_2O_4)_2](NH_4)_3$ (**36**)	DH	1.48	—	H_2O_2	110
$[Ta(O_2)_2(pic)_2]PPh_4$ (**37**)	DH	—	835, 850	H_2O_2	NR[109]
$CrO(O_2)_2py$ (**14**)	PB	1.40	875	H_2O_2	24, OA[111]
$CrO(O_2)_2(Ph_3PO)$ (**38**)	PB	—	945	H_2O_2	HA[80]
$Cr(O_2)_4K_3$ (**39**)	DH	1.49	875	H_2O_2	112
$MoO(O_2)(dipic)(H_2O)$ (**40**)	PB	1.45	900	H_2O_2	NR[113,114]
$MoO(O_2)_2(HMPA)(H_2O)$ (**15**)	PB	1.44	865, 875	H_2O_2	115, 25, SE[116–118]
$MoO(O_2)_2[(S)DML]$ (**41**)	PB	1.45	—	H_2O_2	119, AE[120]
$MoO(O_2)Cl(pic)(HMPA)$ (**42**)	PB	1.41	920	H_2O_2	NR[121]
$Mo(O_2)_2(TPP)$ (**43**)	—	1.4	—	H_2O_2	NR[122]
$WO(O_2)_2(HMPA)(H_2O)$ (**44**)	PB	—	835, 870	H_2O_2	115, SE[123]
$[(WO(O_2)_2)_2O]K_2$ (**45**)	PB	1.5	—	H_2O_2	124
$[WO(O_2)_2(pic)]^-H^+.H_2O$ (**46**)	PB	—	—	H_2O_2	OA[125]
Group VIII metals					
$Ru(O_2)Cl(NO)(PPh_3)_2$ (**47**)	TB	—	875	O_2	126, PO[127]
$Os(O_2)(CO)_2(PPh_3)_2$ (**48**)	—	—	820	O_2	128
$[Co(O_2)(2\text{-phos})_2]BF_4$ (**16**)	TB	1.42	909	O_2	28
$[Co(O_2)(HL)_2]ClO_4$ (**49**)	TB	—	892	H_2O_2	129
$[Rh(O_2)(AsMe_2Ph)_4]ClO_4$ (**50**)	TB	1.46	892	O_2	29, 130, K[131]
$Rh(O_2)Cl(Bu^tNC)(PPh_3)_2$ (**51**)	TB	—	892	O_2	132
$[Ir(O_2)(PMe_2Ph)_4]BF_4$ (**52**)	TB	1.49	838	O_2	29NR[133]
$[Ir(O_2)(dppe)]PF_6$ (**53**)	TB	1.52	—	O_2	134
$Ir(O_2)I(CO)(PPh_3)_2$ (**54**)	TB	1.51	—	O_2	135, OS[136,137], MO[138]
$Ni(O_2)(Bu^tNC)_2$ (**19**)	T	1.45	898	O_2	139, PO[32], I[140]
$Pd(O_2)(PPhBu^t_2)_2$ (**20**)	T	1.37	915	O_2	32
$Pd(O_2)(PPh_3)_2$ (**55**)	T	—	—	O_2	141, 142 MF[143], NR[144]
$Pt(O_2)(PPh_3)_2$ (**21**)	T	1.45	830	O_2	145, PO[146], MF[143,148,149] MO[147,148], SO[150,151]
Actinides					
$UO_2(O_2).4H_2O$ (**56**)	—	—	810	H_2O_2	152, NSE[153]
$UO(O_2)_2(Ph_3PO)_2$ (**57**)	—	—	830	H_2O_2	NR[154]
$Th(O_2)(pic)_2$ (**58**)	—	—	822	H_2O_2	SE[155]

[a] OEP = octaethylporphyrin; (*S*)DML = (*S*)-*N*,*N*-dimethyllactamide; (2-phos) = 1,2-bis(diphenylphosphino)ethylene; HL = 2,2'bipyridylamine.

[b] PB = pentagonal-bipyramidal; PT = pseudotetrahedral; DH = dodecahedral; TB = trigonal bipyramidal; T = trigonal.

[c] NR = nonreactive toward hydrocarbons; PO = oxidation of phosphines to phosphine oxides; MF = peroxometallacyclic adduct formation with cyanoalkenes; NSE = nonstereoselective epoxidation; SE = stereoselective epoxidation; AE = asymmetric epoxidation; HA = hydroxylation of alkanes; HB = hydroxylation of arenes; OA = oxidation of alcohols to carbonyl compounds; K = ketonization of terminal alkenes; SO = oxidation of SO_2 to coordinated SO_4; MO = metallaozonide formation with carbonyl compounds; I = oxidation of isocyanides to isocyanates.

glycol from syngas, or from the hydrogenation of dimethyl oxalate obtained from the palladium-catalyzed carbonylation of methyl nitrite, is the subject of development studies by UCC and UBE.[103,104] The synthesis of acetic anhydride from the carboxylation of methyl acetate (Tennessee Eastman) will compete with the old ketene–acetic acid process,[105] and a new synthesis of vinyl acetate from the reductive carbonylation of methyl acetate to ethylidene diacetate followed by pyrolysis to vinyl acetate is being developed by Halcon.[104] The success of these current and future C_1 processes as alternatives to older oxidation methods will depend on the uncertain changes in crude oil prices.

61.3.2 METAL PEROXIDES IN OXIDATION

Transition metal peroxides, particularly peroxo (**2**), alkylperoxo (**7**) and hydroperoxo (**8**) complexes, are extremely important reactive intermediates in catalytic oxidations involving molecular oxygen, hydrogen peroxide and alkyl hydroperoxides as the oxygen source. Representative peroxo complexes are listed in Table 3, and alkylperoxo and hydroperoxo complexes are listed in Table 4 together with their reactivities.

Table 4 Reactivity of Metal–Alkylperoxo or -Hydroperoxo Complexes[a]

Complex	*Structure*	d(O—O) (Å)	ν(O—O) (cm^{-1})	*Oxygen source*	*Reactivity and/or refs.*
$VO(OOBu^t)(dipic)(H_2O)$	PB	1.436	890	ROOH	NSE, HA, HB[46]
$[MoO(O_2)_2OOH]_2.2(pyH)$	PB	1.46	—	H_2O_2	215
$Co(DMGH)_2(py)(OOCMe_2Ph)$	OH	1.45	—	ROOH	43
Co(salpr)(OO-quinol)	OH	1.50	—	O_2	45
$[Rh(CN)_4(OOH)]K_3$	—	—	825	O_2	216
$RhCl(acac)(OOH)(PPh_3)_2$	—	—	813	O_2	217
$IrCl(OOBu^t)_2(CO)(PPh_3)_2$	—	—	880	ROOH	218
$[Pd(CCl_3CO_2)(OOBu^t)]_4$	—	1.49	855	ROOH	K[42]
trans-$[Pt(Ph)(OOBu^t)(PPh_3)_2]$	SP	—	890	ROOH	K[47,219]
$[Pt(TFA)_2(OOBu^t)(Bu^tOH)]_2$	—	—	870	ROOH	K[220]
$PtMe_2I(OOPr^i)(phen)$	OH	1.465	—	O_2	221
$[Cu_2(OH)_2(OOH)(OAc)]_n$	—	—	820	H_2O_2	222, E[223]

[a] Abbreviations: salpr = five-coordinate Schiff's base; DMGH = dimethylglyoximate; OH = octahedral; SP = square planar; E = epoxidation of alkenes. The other abbreviations are the same as in Table 3.

Peroxide complexes are potential oxygen donors to organic substrates, but only a few of them are reactive. This reactivity depends on physical criteria, such as solubility in organic substrates, and on chemical criteria, *va.* the nature of the metal, the geometry of the complex, the availability of vacant or releasable coordination sites for the complexation of the substrate, and the overall charge of the reagent. Three reactivity zones can be schematically distinguished: (i) Mo^{VI}- and W^{VI}-peroxo complexes, which act as heterolytic alkene epoxidation reagents: (ii) V^V-peroxo and -alkylperoxo complexes and Cr^{VI}-peroxo complexes, which act as homolytic hydroxylation reagents; and (iii) Rh^{III}-peroxo complexes and alkyl- or hydro-peroxo complexes of Rh^{III}, Ir^{III}, Pd^{II} and Pt^{II}, which act as heterolytic alkene ketonization reagents.

61.3.2.1 Metal–Peroxo Complexes

61.3.2.1.1 Molybdenum and Tungsten

(i) Stoichiometric oxidations

Molybdenum(VI)- and tungsten(VI)-oxodiperoxo complexes of general formula $MO(O_2)_2L_1L_2$ (M = Mo, W; L_1, L_2 = organic bases) are well-defined crystalline compounds, soluble in organic solvents, and easily prepared by the addition of a basic ligand to a solution of MoO_3 or WO_4H_2 in hydrogen peroxide.[115] These complexes transfer oxygen atoms to a variety of reactive substrates.

Epoxidation of alkenes by $MoO(O_2)_2(HMPA)(H_2O)$ (**15**) has been shown to proceed *via* two steps: reversible complexation of alkene to the metal, displacing the equatorial HMPA ligand, followed by irreversible oxygen transfer to the alkene.[116–118] This reaction has the following

characteristics:

(1) The reactivity of alkenes increases with their nucleophilic nature in the order tetrasubstituted > trisubstituted > disubstituted > monosubstituted. Further, the epoxidation rate $V = k_2K[\text{alkene}][\text{complex}]/(1 + K[\text{alkene}])$ shows that decomposition of the alkene-metal complex represents the rate determining step in this reaction.

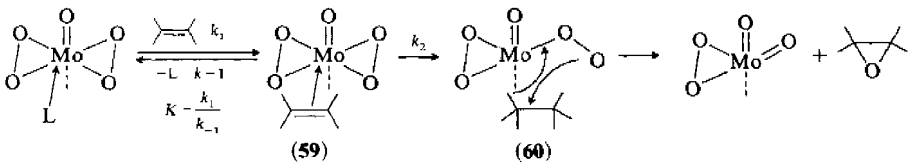
(2) Oxygens atoms incorporated in the alkene are of peroxide origin only.[117]

(3) The epoxidation of alkenes is completely stereoselective, *i.e.* *cis*-alkenes are transformed into *cis*-epoxides and *trans*-alkenes into *trans*-epoxides.

(4) The epoxidation of alkenes is strongly retarded by σ-donor ligands such as DMF or HMPT which prevent complexation of the alkene on the metal.[116,121]

(5) The alkene requires a releasable coordination site adjacent and coplanar to the peroxo moiety for the epoxidation to occur. Table 3 shows that complexes (**40**) and (**42**) having such positions occupied by anionic ligands or strongly complexing bidendate or tridendate ligands which cannot be displaced by the alkene are completely inactive. On the other hand, the coordinatively saturated bis(hydroxamato) complex $MoO(O_2)\{PhCON(Ph)O\}_2$ is reluctant to react with simple alkenes but, in a highly stereospecific way, epoxidizes allylic alcohols which can displace hydroxamato ligands on the metal (*e.g.* cyclohexen-3-ol is exclusively transformed into *cis*-1,2-epoxycyclohexan-3-ol).[156]

All these data are consistent with the cyclic peroxymetalation mechanism of epoxidation shown in equation (26).

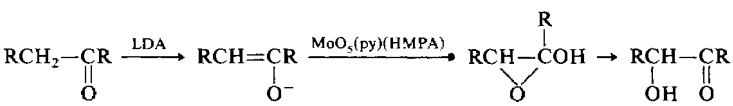


(59) (60) (26)

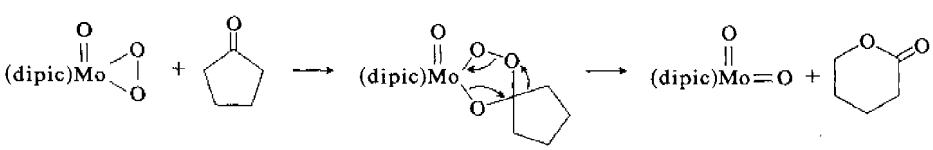
The nature of the alkene-metal association in complex (**59**) is a pure Lewis base–Lewis acid bond, since Mo^{VI} has no *d*-electrons available for back-bonding to the alkene. The alkene, becoming electrophilic after its complexation to the metal, is then attacked by the nucleophilic peroxide oxygen atom according to an intramolecular 1,3-dipolar mechanism, transiently giving a five-membered dioxametallacycle which decomposes by 1,3-dipolar cycloreversion to produce the epoxide and the oxo complex. This mechanism, which has recently received theoretical support,[157] is perfectly consistent with the π–σ rearrangement (*cis* insertion) which occurs in most transition metal-catalyzed transformations of alkenes.[158] The cyclic peroxymetalation mechanism is somewhat similar to the dimerization of two coordinated alkenes at a metal center involving formation of metallacyclopentanes.[159] Stable dioxametallacyclic adducts have been obtained from the reaction of tetracyanoethylene with the titanium-peroxo complex $Ti(O_2)$-$(pic)_2(HMPA)$ (**32**),[106] and are commonly synthesized from the addition of cyanoalkenes or ketones to Group VIII peroxo complexes.

Asymmetric epoxidation of simple alkenes (*e.g.* propene, *trans*-2-butene) has been achieved stoichiometrically using MoO_5 complexes bearing chiral bidendate ligands such as (*S*)-*N*,*N*-dimethyllactamide, with enantiomeric excess of up to 35%.[119,120,160,161] Since MoO_5 peroxo complexes bearing chiral monodendate ligands exhibit no asymmetric induction, it was assumed that the origin of this asymmetric induction is that *N*,*N*-dimethyllactamide remains axially coordinated *via* the hydroxyl group during this reaction, while the equatorial carbonyl group is displaced by the alkene.[162]

Molybdenum-peroxo compounds have been shown to achieve a variety of selective oxidations: they α-hydroxylate enolizable ketones, presumably *via* epoxidation of the enolate (equation 27);[163] they cause Baeyer-Villiger lactonization of cyclic ketones, probably *via* the formation of five-membered trioxametallacycles (equation 28);[164] they oxidize alcohols to carbonyl compounds

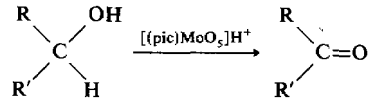


(27)



(28)

(equation 29),[125,156] *n*-butyllithium,[165] alkylboron[166] and magnesium[167] compounds to alcohols, amides to hydroxamic acids,[168,169] and nitro compounds to carbonyl compounds.[170] All these reactions proceed with high selectivity.

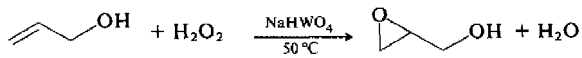


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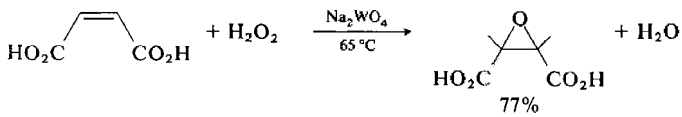
Tungsten(VI)-peroxo complexes such as $WO(O_2)_2(HMPA)(H_2O)$ are also effective reagents for the selective transformation of alkenes to epoxides. *cis*-Alkenes such as *cis*-2-butene are exclusively converted to *cis*-epoxides.[123]

(ii) Catalytic oxidations by hydrogen peroxide

Molybdenum and tungsten compounds have long been known to catalyze the transformations of alkenes into epoxides and diols by hydrogen peroxide.[171–173] This reaction was found to be suitable for the epoxidation of water-soluble alkenes such as allylic alcohols (equation 30)[174,175] or unsaturated carboxylic acids (equation 31).[171] Tungsten catalysts were found to be more active and selective in aqueous solution than molybdenum complexes.



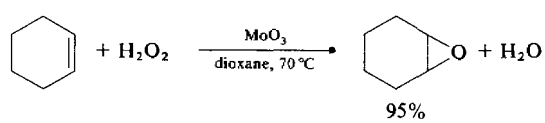
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(31)

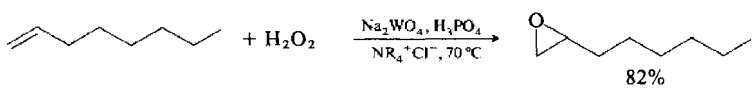
The epoxidation of water-insoluble alkenes requires the use of polar cosolvents (alcohols, dioxane, amides), which inhibit the reaction however, and the primary epoxide products are easily hydrolyzed in the presence of water to give the corresponding glycols.

A major improvement consisting of the continuous removal of the water (introduced with H_2O_2 and coproduced during the reaction) by azeotropic distillation considerably increased the yield of the epoxidation reaction (equation 32).[176] Under anhydrous conditions, molybdenum catalysts were found to be superior to tungsten catalysts, as expected by the comparative stoichiometric reactivity of MoO_5 and WO_5 complexes.



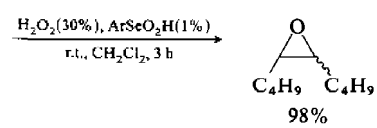
(32)

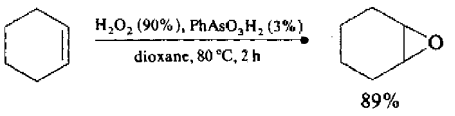
It was recently shown that alkenes can be epoxidized in a highly effective way by diluted H_2O_2 under phase-transfer conditions in the presence of Na_2WO_4 and H_3PO_4 or $NaHAsO_4$ under acidic conditions. Even nonreactive terminal alkenes such as 1-octene could be effectively transformed under these conditions (equation 33).[177]



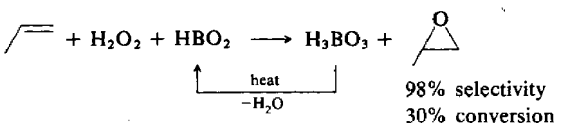
(33)

It is noteworthy that selenium, arsenic and boron compounds are also effective catalysts for the selective epoxidation of alkenes by H_2O_2 (equations 34–36). It is generally thought that peroxyselenic[178,179] and peroxyarsonic acids[180,181] act as reactive intermediates in a way similar to that of peroxycarboxylic acids. Metaboric acid, HBO_2, acts as both an epoxidation catalyst and a dehydrating agent. The resulting orthoboric acid can be dehydrated back to metaboric acid.[176]





89% (35)



98% selectivity
30% conversion (36)

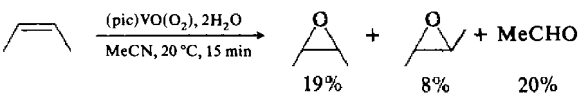
61.3.2.1.2 Vanadium and chromium

(i) Homolytic oxidation of hydrocarbons by vanadium(V)-peroxo complexes

Covalent vanadium(V)-peroxo complexes of general formula $VO(O_2)(pic)L_1L_2$ (L_1, $L_2 = H_2O$ or basic ligands) and ionic complexes with the formula $[VO(O_2)(pic)_2]^-A^+(A^+ = H^+, PPh_4^+)$ can easily be synthesized from V_2O_5, H_2O_2, picolinic acid and ligands. These complexes exhibit a different behavior from that of Mo^{VI}- and W^{VI}-peroxo complexes.[22]

(1) Although stable in protic solvents (H_2O, MeOH), they decompose homolytically in nonprotic solvents (CH_2Cl_2, MeCN) to give O_2 and the corresponding V^V-dioxo complexes. The reactivity of V^V-peroxo complexes toward hydrocarbons parallels their decomposition rate in nonprotic solvents, with the most reactive compounds being $VO(O_2)(pic)(H_2O)_2$ (**12**) and $[VO(O_2)(pic)_2]^-H^+ \cdot HMPA$.

(2) In nonprotic solvents, alkenes are stoichiometrically oxidized by V^V-peroxo complexes to epoxides and consecutive oxidative cleavage products in a nonstereoselective fashion. For example, *cis*-2-butene gave an approximately 2:1 mixture of *cis*- and *trans*-epoxides (equation 37). The reactivity of alkenes increases with their nucleophilic nature. Alkenes containing phenyl substituents such as styrene, α- and β-methylstyrene are also very reactive and mainly give oxidative cleavage products.



19% 8% 20% (37)

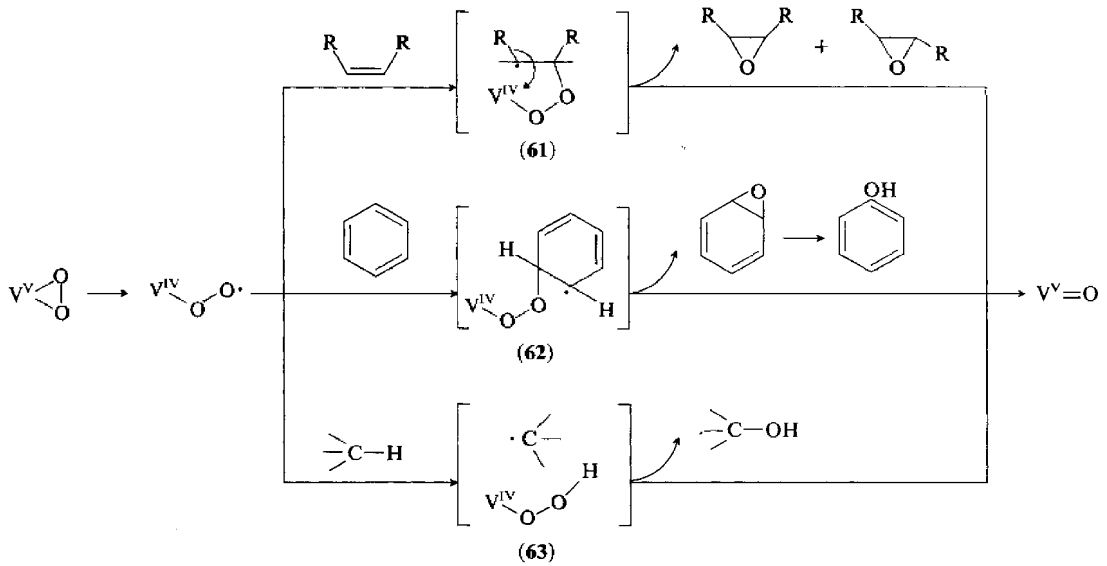
(3) Aromatic hydrocarbons are mainly hydroxylated to phenolic products. Complex (**12**) hydroxylated benzene in MeCN at 20 °C into phenol in *ca.* 55% yield, and no isotope effect was found for this reaction. Hydroxylation of toluene mainly occurs at the ring positions, with minor amounts of benzylic oxidation products. Hydroxylation of 4-deuterotoluene by (**12**) occurred with 70% retention and migration of deuterium in the formation of *p*-cresol. This high NIH shift value is in the same range as that found for liver microsome cytochrome *P*-450 hydroxylase, and suggests the transient formation of arene oxide intermediates.

(4) Hydroxylation of alkanes preferentially occurs at the more nucleophilic C—H bonds, with a relatively low isotope effect ($kH/kD = 2.8$ for cyclohexane) and a significant amount of epimerization at the hydroxylated carbon atom. Radical carbon intermediates were revealed in this reaction by trapping experiments with chlorine atoms coming from CCl_4.

(5) In contrast to Mo-peroxo complexes, basic ligands such as HMPA have no or little inhibitory effect on the oxidation rates by V^V-peroxo complexes.

The reactivity of V^V-peroxo complexes, which is different from and much less selective than that of Mo- and W-peroxo complexes, was tentatively attributed to a biradical $V^{IV}—O—O\cdot$ species resulting from the homolytic cleavage of the $V^V—O$ (peroxo) bond, as shown in Scheme 2. The biradical $V^{IV}—O—O\cdot$ species could: (a) add to double bonds to give a freely rotating free radical intermediate (**61**), which homolytically decomposes to an epoxide mixture and V^V-oxo compound; (b) add to aromatic rings to give the intermediate (**62**), which decomposes to phenol *via* arene oxide; or (c) abstract a hydrogen atom from alkanes to give an intermediate carbon radical (**63**), followed by a recombination with the hydroxyl radical coming from $V^{IV}—OOH$ to give the alcohol and the V^V-oxo complex.

In this case, no complexation of the substrate on the metal occurs, and the oxidation results from the bimolecular electrophilic attack of the radical terminal oxygen atom on the hydrocarbon,

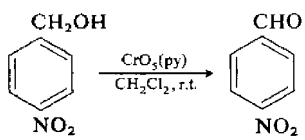


Scheme 2 Mechanism of Hydrocarbon Oxidation by V^V-Peroxo Complexes

but as this reaction occurs outside the coordination sphere of the metal, the selectivity of the reaction is lower.

(ii) Oxidation of hydrocarbons by chromium(VI)-peroxo complexes

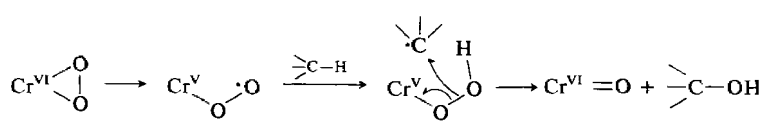
The reactivity of $CrO(O_2)_2L$ (L = basic ligand) towards hydrocarbons strongly differs from that of the structurally analogous MoO_5 and WO_5 complexes, and from that of V^V-peroxo complexes. The complex CrO_5py selectively oxidizes alcohols to carbonyl compounds with high yields (equation 38).[111] These complexes, *e.g.* $CrO_5(Ph_3PO)$ (**38**), are reluctant to epoxidize alkenes and to hydroxylate arenes. Instead, they oxidize aliphatic C—H bonds into alcohols and carbonyl compounds.[80] The most reactive hydrocarbons were found to be those having labile allylic and benzylic C—H bonds. Cyclohexene gave high yields of cyclohexen-3-ol and cyclohexen-3-one with no epoxide formation, and tetralin gave 2-tetralone as the major oxidation products.



90% (38)

The other alkanes were found to be much less reactive. Cyclohexane gave a cyclohexanol-one mixture, and adamantane was preferentially hydroxylated at the tertiary positions; *cis*-decalin gave a mixture of *cis*- and *trans*-9-decanol (together with 1- and 2-decalones), suggesting the transient formation of radical carbon intermediates, which were also revealed by trapping experiments with CCl_4.

It is noteworthy that the reactivity of hydrocarbons towards $CrO_5(Ph_3PO)$ parallels their reactivity toward $RO_2\cdot$ radicals for hydrogen abstraction. This suggests that Cr^{VI}-peroxo complexes almost exclusively act as hydrogen atom abstractors, in their homolytically dissociated form Cr^V—$OO\cdot$ (equation 39).[80]

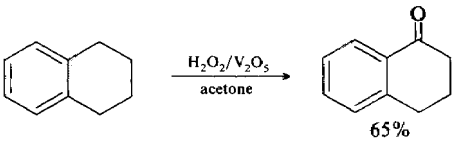


(39)

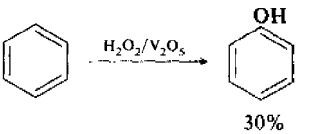
(iii) Catalytic oxidation by H_2O_2

The easy regeneration of V^V- and Cr^{VI}-peroxo species from the reaction of oxo species with hydrogen peroxide enables the catalytic oxidation of the hydrocarbon to occur. However, the synthetic usefulness of these reactions is limited by the parallel catalytic decomposition of H_2O_2 associated with the decomposition of the peroxo species, and by the consecutive oxidation of the

oxygenated products. Some examples of the catalytic oxidation of tetralin[182] and benzene[183] are given in equations (40) and (41).



(40)



(41)

61.3.2.1.3 Group VIII metals

As shown by Table 3, most of the Group VIII metal-peroxo complexes are obtained from the direct interaction of dioxygen with the corresponding reduced forms. A considerable effort has been devoted to this subject in the last decade with the hope that selective oxidations of hydrocarbons could be achieved by the activation of molecular oxygen under mild conditions[12,56,133,184] and several such examples have actually been shown to occur.

Group VIII metal-peroxo complexes generally act as 1,3-dipolar reagents $M^+—O—O^-$ in which the positive charge is localized on the metal and the negative charge on the terminal oxygen atom of the peroxo group. They undergo a series of reactions with both nucleophilic and electrophilic substrates. Some examples of stoichiometric reactions of the well-known $PtO_2(PPh_3)_2$ complex are shown in Figure 2.[184]

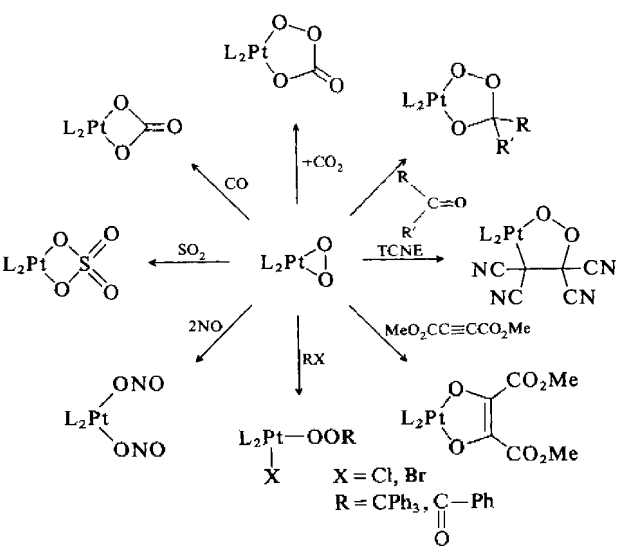
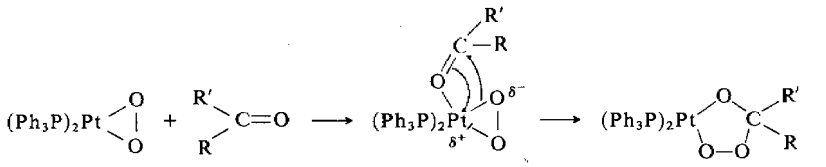


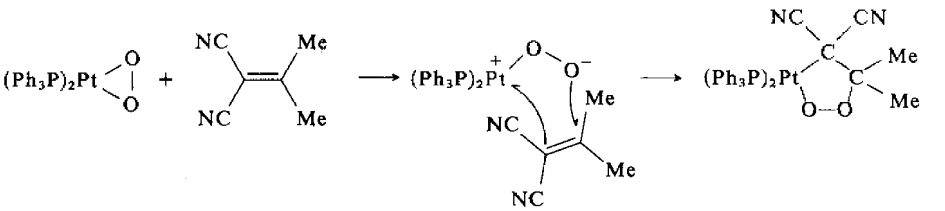
Figure 2. Reactions of $(PPh_3)_2PtO_2$

Stable five-membered dioxametallacyclic adducts are obtained from the reaction of Group VIII metal-peroxo complexes (Rh, Ir, Pd, Pt) with nucleophilic ketones[147] and electrophilic alkenes[188,143] or ketones.[148,186,138] The adducts of $PtO_2(PPh_3)_2$ with acetone[185] and 1,1-dicyano-2-methylpropene[187] have been characterized by X-ray crystallography. The reaction of $(Ph_3P)_2PtO_2$ with nucleophilic ketones involves, as the major pathway, the precoordination of the carbonyl compound to the vacant axial site of platinum prior to intramolecular 1,3-dipolar cycloaddition (equation 42).[147,148]

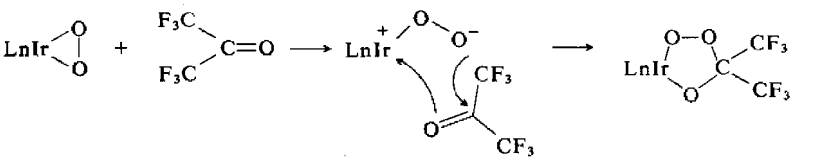


(42)

In the case of electrophilic substrates, the peroxometallic adduct results from the bimolecular 1,3-dipolar cycloaddition of the peroxo moiety to a cyanoalkene (equation 43)[143,188] or a fluoroketone (equation 44).[138]



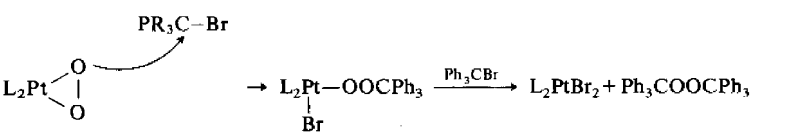
(43)



(44)

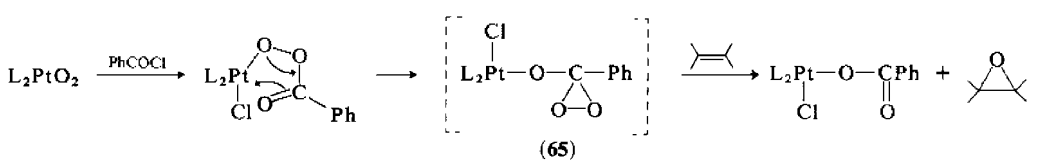
In contrast to CO_2,[189] SO_2,[132] and the previously described substrates which insert into the metal-oxygen bond, electrophilic alkynes such as dimethyl acetylenedicarboxylate insert into the O—O bond (Figure 2).[44,190]

The reaction of $PtO_2(PPh_3)_2$ with alkyl halides results in the formation of alkylperoxo complexes, presumably *via* an S_N2 nucleophilic attack of the terminal oxygen on the carbon atom, and occurs with inversion of configuration.[44] Addition of excess alkyl halide to the alkylperoxo complex results in the formation of the dialkyl peroxide (equation 45).[44]



(45)

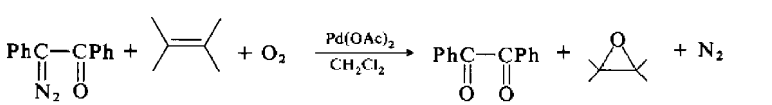
Benzoyl chloride reacts with $PtO_2(PPh_3)_2$ to give an isolated acylperoxy-platinum complex capable of epoxidizing alkenes such as cyclohexene or norbornene with *ca.* 50% yield.[191,44] Owing to the low coordinating ability of cyclohexene to platinum, a reactive dioxirane intermediate (**65**) could be suggested as the actual epoxidizing agent, by analogy with the reactivity of diaroyl peroxides (equation 46).[192,193]



(46)

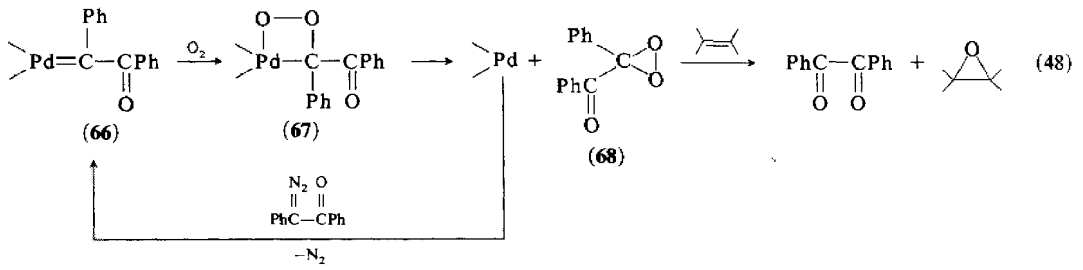
(**65**)

A related epoxidation reaction was found to occur catalytically when an alkene was reacted with azobenzil in the presence of O_2 and catalytic amounts of palladium acetate (equation 47).[194]



(47)

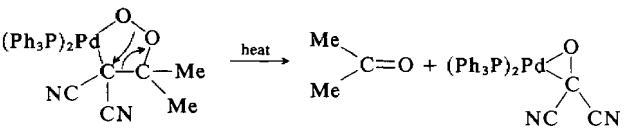
Either a palladadioxetane species (**67**) formed upon addition of O_2 to the ketocarbene metal complex (**66**), or a dioxirane form (**68**), has been suggested to be the active intermediate in this reaction (equation 48).



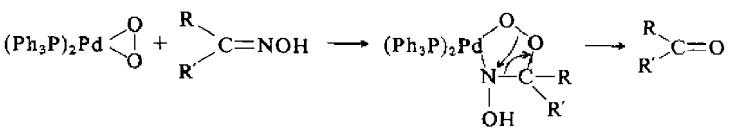
(48)

It is noteworthy that $PtO_2(PPh_3)_2$ can oxidize benzyl to benzoic anhydride with 55% yield by inserting one oxygen atom between the two carbonyl groups.[195]

The palladium peroxometallic adducts were found to be less stable than the platinum analogs and decompose mainly by C—C bond cleavage to carbonyl compounds (equation 49).[143] A similar decomposition may occur in the oxidation of ketoximes to ketones by $PdO_2(Ph_3P)_2$ (equation 50).[195]

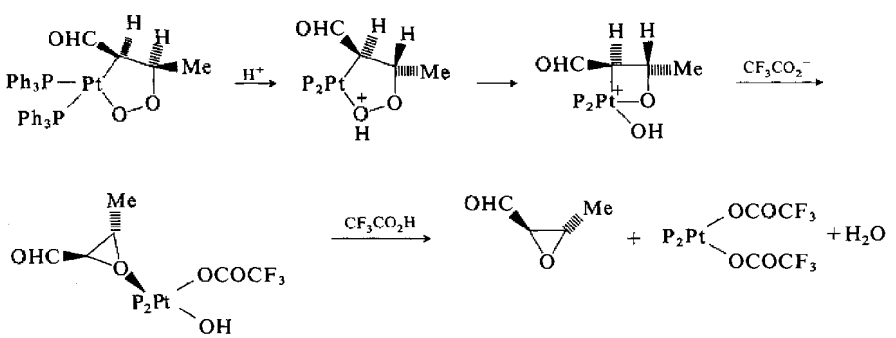


(49)



(50)

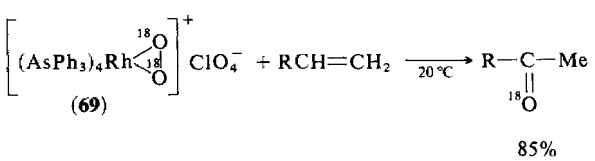
The addition of trifluoroacetic acid to the palladium or platinum peroxide adducts with electrophilic alkenes results in the formation of epoxide in high yield and with high stereoselectivity.[143,148] The mechanism shown in equation (51) has been suggested for this reaction.[148]



(51)

A large number of Group VIII metal–dioxygen complexes catalyze the oxidation of phosphine to phosphine oxide or isocyanides to isocyanates by molecular oxygen.[6,12,56,140,141,146,184] However, their use as catalysts for the oxidation of alkenes generally leads to the same products as those obtained from free radical chain autoxidations.[184,196–198]

With the notable exception of rhodium, Group VIII metal–peroxo complexes are generally reluctant to react with simple alkenes by nonradical pathways. However, such an oxygen transfer has been shown to occur in the reaction of ^{18}O-labeled $[(AsPh_3)_4RhO_2]^+ClO_4^-$ with terminal alkenes under O_2-free, anhydrous conditions, producing ^{18}O-labeled methyl ketone (equation 52).[131]



(52)

This oxygen-transfer reaction was based on an important observation by Read *et al.*, who found that rhodium complexes such as $RhCl(PPh_3)_3$ were able to promote the cooxygenation of terminal

alkenes to methyl ketones and PPh_3 to Ph_3PO using conditions under which a Wacker-type oxidation (hydroxymetalation of the coordinated alkene by water) was disfavored (equation 53).[199]

$$RCH{=}CH_2 + PPh_3 + O_2 \xrightarrow[C_6H_6]{RhCl(PPh_3)_3} R{-}\underset{\underset{O}{\|}}{C}{-}Me + Ph_3PO \qquad (53)$$

In this reaction, one oxygen atom of the dioxygen molecule is incorporated into the alkene, while the phosphine acts as a coreducing agent with the second oxygen atom to produce phosphine oxide. In the absence of phosphines and under more forced conditions, the use of Rh^I complexes as catalysts for the autoxidation of alkenes results in the formation of the expected ketone together with allylic or cleavage oxygenated products, presumably coming from parallel radical chain reactions.[198,200–203]

The use of rhodium trichloride associated with copper(II) perchlorate or nitrate in an alcoholic solvent resulted in a major improvement in the catalytic oxidation of terminal alkenes by O_2 at room temperature, without the need for a coreducing agent (equation 54).[204]

$$2RCH{=}CH_2 + O_2 \xrightarrow[EtOH,\ 20\text{–}80\,^\circ C]{RhCl_3 + Cu(ClO_4)_2} 2R{-}\underset{\underset{O}{\|}}{C}{-}Me \qquad (54)$$

$\geq 98\%$

In this reaction, both oxygen atoms are incorporated into two moles of alkene to give two moles of ketone with a selectivity, based on consumed alkene and O_2, of up to 98%. The characteristics of the reaction are different from conventional Wacker chemistry.

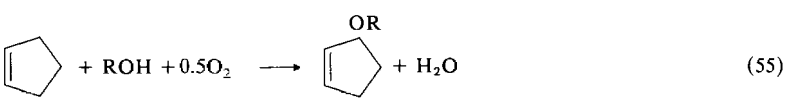
(1) In contrast to the corresponding palladium system, water is not involved as the oxygen source. In fact it is an inhibitor, and the presence of a dehydrating agent such as 2,2-dimethoxypropane speeds up the reaction.

(2) Although the alcohol solvent does not act as a coreducing agent, it is necessary for the reaction and probably intervenes in the formation of the active species.[204,205]

(3) The presence of copper(II) salts, in the optimum ratio Cu:Rh = 1 or 2, considerably increases the rate and the selectivity of the reaction. Rhodium perchlorate alone acts as a catalyst, but cooxidizes the solvent alcohol to a carbonyl compound. With Cu:Rh = 1, 85% of the copper precipitates from the reaction mixture as CuCl.

(4) The presence of chloride anions in an optimum ratio Cl:Rh = 2 or 3 and an acidic medium (H^+:Rh = 3) are necessary for the reaction.[204,207]

(5) The nature of the oxidation products is traceable to the nature of the rhodium–alkene interaction. Terminal alkenes and internal ones (*e.g.* cycloheptene), which form π-complexes of rhodium(I), *e.g.* $[RhCl(alkene)_2]_2$, are selectively converted into methyl ketones, whereas alkenes which form π-allylic complexes of rhodium(III) (*e.g.* cyclopentene) give alkenyl ethers *via* oxidative substitution of the alkene by the solvent alcohol.[204]

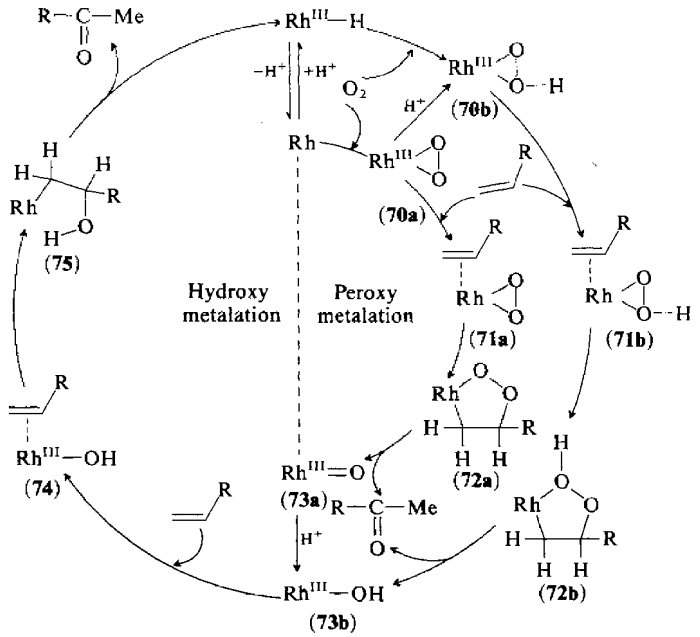


(55)

(6) The $RhCl_3$–$Cu(ClO_4)_2$ catalyzed oxidation of 1-hexene is first-order dependent on rhodium and alkene concentration, and independent of dioxygen pressure. In fact, higher O_2 partial pressure inhibits the reaction. Strongly complexing alkenes, *e.g.* cyclooctene, were found to be less reactive than terminal ones. Further, the reaction is strongly inhibited by ligands, *e.g.* PPh_3, or strongly complexing dialkenes, *e.g.* 1,5-cyclooctadiene.

The overall catalytic oxidation of terminal alkenes to methyl ketones by O_2 has been tentatively interpreted as resulting from the consecutive consumption of each oxygen atom by two moles of alkene in two complementary reactions as shown in Scheme 3.

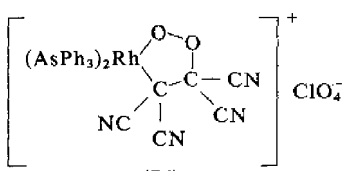
The first peroxide oxygen atom is transferred to the alkene by a peroxymetalation pathway involving coordination of both O_2 and alkene to the metal in (**71a**) or (**71b**), followed by the formation of a peroxometallacycle (**72a**) or (**72b**) which decomposes to give the methyl ketone and the rhodium-oxo (**73a**) or -hydroxo (**73b**) species. The second hydroxo oxygen atom is transferred *via* an internal *cis* hydroxymetalation mechanism (Wacker type), which produces a second mole of ketone and regenerates the initial Rh^{III} hydride or the Rh^I species by reductive elimination of the latter. Two plausible alternative versions of the peroxymetalation pathway can be envisaged[133] and these are described below.



Scheme 3

(1) The cyclic peroxymetalation process (inner half-circle of Scheme 3) involves the peroxo species (**70a**) as the reactive intermediate. The cyclic adduct (**72a**) can result (a) from the reaction of an Rh^{III}-peroxo complex with an alkene or (b) from the reaction of an Rh^{I}-π-alkenic complex with O_2. Indeed, both of these reactions (a) and (b) have been shown to occur.

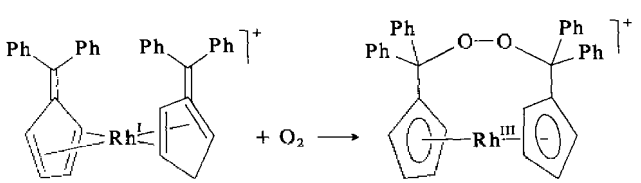
(a) As previously shown in equation (52), the Rh^{III}-peroxo complex (**69**) selectively oxidizes terminal alkenes with methyl ketones. In contrast, the complex $[RhO_2(dppe)_2]^+ClO_4^-$ was found to be inactive, illustrating that it is necessary to to be able to create a coordination site for the alkene at rhodium. Further, an Rh^{III} peroxometallacycle (**76**) from the reaction of (**69**) with tetracyanoethylene has been characterized.[131]



(**76**)

(b) The Rh^{I}-π-alkenic complex $[Rh(1,7\text{-octadiene})_2]^+BF_4^-$ in anhydrous isopropyl alcohol absorbs 1 mole of O_2 per mole of rhodium, and produces *ca.* 1 mole of 7-octen-2-one and 1 mole of water. In the presence of 1 equivalent of HBF_4 and a large excess of 1,7-octadiene, more than 1 mole of O_2 was absorbed per mole of rhodium, whereas neither water nor acetone (from isopropyl alcohol used as solvent) was produced. Under these conditions, both atoms of O_2 were incorporated into 2 moles of alkene and the production of 7-octen-2-one was slightly catalyzed.[131]

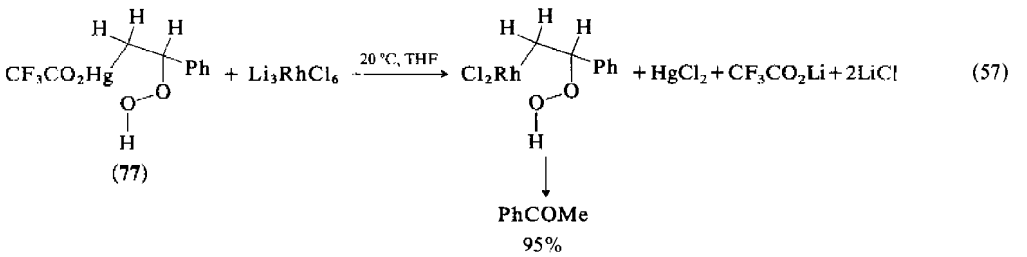
It is noteworthy that the reaction of $[Rh(dpf)_2]^+ClO_4^-$ (dpf = 6,6-diphenylfulvene) with O_2 results in the formation of a coordinated peroxide by insertion of O_2 between the two ligands (equation 56).[208]



(56)

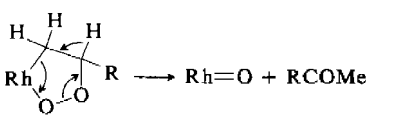
(2) The pseudocyclic peroxymetalation process (outer half-circle of Scheme 3) involves the protonated hydroperoxo intermediate (**70b**) as the reactive intermediate and appears more likely

to occur in the $RhCl_3$–$Cu(ClO_4)_2$ catalyzed ketonization of terminal alkenes.[133,205,207] Drago and coworkers have shown that rhodium–hydroperoxo species can be formed from *in situ* H_2O_2 generated from reduction of O_2 by alcohol in the presence of H^+, Cu^{II} and Rh^{III}.[205] In further support of this process, the transmetalation of mercury by rhodium in complex (**77**) results in the formation of acetophenone in 95% yield (equation 57).[133] The pseudocyclic hydroperoxymetalation mechanism will be discussed in more detail in the following section.

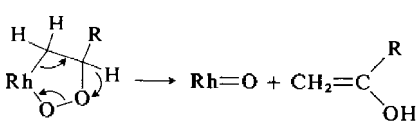


(57)

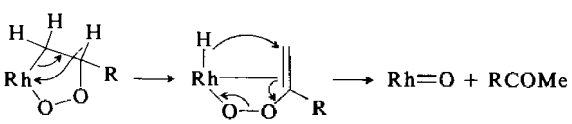
The decomposition of the peroxometallacycle (**72a**) or (**72b**) occurs in a way different from that previously shown to occur in the epoxidation of alkenes by molybdenum–peroxo complexes (equation 26). The three possibilities are shown in equations (58)–(60) and involve: (a) a [C-β, C-α] hydride shift which directly produces the methyl ketone and the rhodium–oxo complex, or the hydroxo species from (**72b**; equation 58); (b) a [C-β, O-β] hydride shift which gives enol (equation 59). The decomposition mode is somewhat similar to that previously shown in equation (28) for the Baeyer–Villager oxidation of ketones by Mo–peroxo complexes; (c) a β-hydride abstraction by rhodium followed by a nucleophilic attack at the coordinated alkene by the hydride (equation 60), as suggested for the Wacker process[209] and the ketonization of alkenes by palladium–nitro complexes.[210] Although reactions (58) and (60) cannot be ruled out for the decomposition of pseudocyclic palladium peroxometallacycles (*vide infra*), a [C,O] hydride shift appears more likely to occur in the Rh–Cu catalyzed ketonization of alkenes, owing to the substantial incorporation of EtOD deuterium in the resulting ketone.[211]



(58)



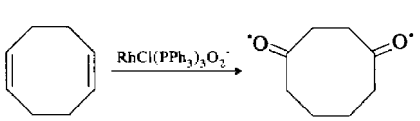
(59)



(60)

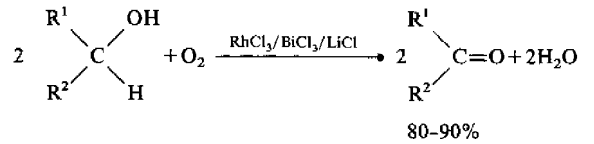
The highly beneficial effect of copper salts on the activity and selectivity of the rhodium catalyst still remains poorly understood. One of the likely hypotheses is that Cu^I reduces O_2 to form $Cu_2O_2^{2+}$ which favors the formation of the active rhodium–hydroperoxo species.[207]

As recently reported, rhodium–dioxygen complexes such as $RhCl(O_2)(PPh_3)_2$ can transfer both dioxygen atoms to one mole of coordinated 1,5-cyclooctadiene to give cyclooctane-1,4-dione, without the intermediate formation of monoketone (equation 61). In the presence of excess PPh_3, the reaction becomes slightly catalytic.[212]



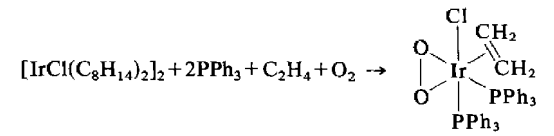
(61)

Associated with $BiCl_3$ and LiCl, $RhCl_3$ acts as a very effective catalyst for the selective oxidation of secondary alcohols to carbonyl compounds by O_2 under mild conditions. Selectivities up to 90% and turnovers numbering up to 200 have been obtained (equation 62).[213]



(62)

Iridium-peroxo complexes behave very differently from the rhodium analogs. The complex $[IrO_2(AsPhMe_2)_4]^+ClO_4^-$ was found to be inactive towards alkenes, and the complex $[Ir(C_8H_{14})_4]^+BF_4^-$ absorbs one mole of O_2 per mole of iridium, but does not produce cyclooctanone.[133] It is noteworthy that a stable iridium complex having both ethylene and O_2 coordinated to the same metal has been synthesized, without any oxygen transfer reaction occurring in this case (equation 63).[214]



(63)

It therefore appears that coordination of alkene and dioxygen on the same metal center is a necessary but not sufficient condition for achieving an oxygen transfer reaction from Group VIII dioxygen complexes. Suitable positions for both alkene and O_2 are also required, probably coplanar and adjacent in the coordination sphere of the metal.

61.3.2.2 Alkylperoxo and Hydroperoxo Complexes

Clearly identified μ-peroxo complexes are much less numerous than peroxo complexes, and are listed in Table 4 together with their reactivity. Although their structural characteristics are generally different from those of peroxo complexes, their reactivity appears to be very close to them in both stoichiometric and catalytic conditions.

61.3.2.2.1 d^0 Metal–alkyl peroxides

High-valent d^0 transition metal complexes, *e.g.* complexes of Mo^{VI}, V^V and Ti^{IV}, catalyze numerous oxidations of organic substrates by alkyl hydroperoxides, such as epoxidation of alkenes, oxidation of tertiary amines to the corresponding *N*-oxides, of sulfides to sulfoxides, *etc.*[56,57,100,184,224-228] It is now generally understood that the active intermediates in these transformations consist of d^0 metal-alkyl peroxide complexes M—OOR in their triangular form (**7a**) resulting from anion exchange on the metal by the alkyl hydroperoxide (equation 10).[121,229,230] With the exception of the recently reported dipicolinatovanadium(V)-alkyl peroxides,[46] these compounds have proved difficult to synthesize. Hence, a good correlation between stoichiometric reagents and catalytic oxidations appears to be less easy to make than for peroxo complexes.

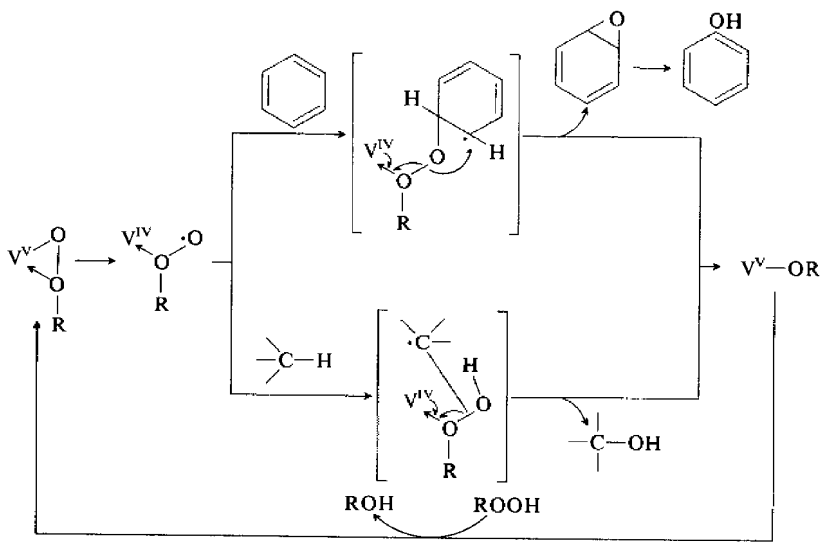
(i) Oxidation of hydrocarbons by VO(dipic)(OOR)L[46]

These complexes are easily prepared from the reaction of *t*-butyl hydroperoxide (TBHP) or cumyl hydroperoxide with the V^V-oxohydroxo complex (equation 10). The X-ray structure of VO(dipic)($OOBu^t$)(H_2O) (**22**) revealed a pentagonal bipyramidal environment with an O—O triangularly bonded *t*-butyl peroxide group. This structure is comparable with that of the V^V-peroxo complex $[VO(O_2)(dipic)(H_2O)]NH_4$[231] and the V^V-*O,N*-hydroxylamino complex VO(dipic)-(ONH_2)(H_2O).[232]

The reactivity of (**22**) was found to be similar to that of V^V-peroxo complexes[22] with, however, some significant differences. (a) Alkenes are poorly and nonstereospecifically epoxidized, and mainly give allylic and cleavage oxygenated products. (b) Benzene is hydroxylated to phenol, and alkylbenzenes (*e.g.* toluene, ethylbenzene) give a mixture of nuclear and side-chain hydroxylation products (V^V-peroxo complexes essentially gave phenolic products). Hydroxylation of 4-deuterotoluene occurs with a high (62%) NIH shift value in the formation of *p*-cresol. (c) Hydroxylation of alkanes occurs with a significant amount of epimerization at the hydroxylated carbon atom. Further, carbon radical intermediates were also revealed by trapping experiments with chlorine atoms coming from CCl_4.

All these data are in favor of a homolytic mode of oxygen transfer from V^V alkyl peroxides to hydrocarbons, and the mechanism suggested in Scheme 4, based on that of oxidation by V^V-peroxo complexes (Scheme 2), was tentatively attributed to a biradical $V^{IV} \leftarrow OR—O\cdot$ species which can add to arenes and abstract hydrogen atoms from alkanes. It is probable that the absence of a releasable coordination site adjacent to the triangular alkyl peroxide group in (**22**) precludes the possibility of the alkene coordination to the metal and therefore prevents its heterolytic epoxidation.

In the presence of excess TBHP, the hydroxylation of cyclohexane by (**22**) becomes catalytic.[46]

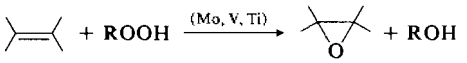


Scheme 4

It was also recently shown that $VO(OBu^t)_3$ catalyzes the oxidation of *n*-octane by TBHP to a mixture of isomeric octanones with yields close to 80%, and reactive V^V *t*-butyl peroxides have been detected as intermediates.[233]

(ii) Epoxidation of alkenes by alkyl hydroperoxides catalyzed by d^0 metal complexes

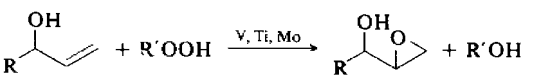
The selective epoxidation of alkenes by alkyl hydroperoxides in the presence of d^0 transition metals (equation 64), reported in 1965,[234] has been widely applied in organic chemistry and has been developed into a commercial process for the manufacture of propylene oxide by Halcon (M = Mo)[99] and by Shell ($M = Ti/SiO_2$).[100]



(64)

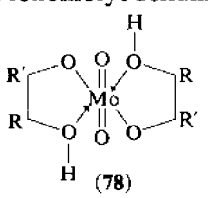
The reaction has the following characteristics.[56,57,100,184,224–228]

(*a*) *Catalysts.* Molybdenum compounds, *e.g.* $Mo(CO)_6$, MoO_2X_2 (X = Cl, acac, stearate, 8-hydroxyquinolinate, *etc.*), $MoCl_5$, are the best catalysts for the epoxidation of simple alkenes, while vanadium compounds have a much lower ($\sim 10^2$) activity, as do soluble titanium compounds.[235] However, vanadium and titanium complexes are more selective and sometimes more active catalysts than molybdenum for the epoxidation of allylic alcohols (equation 65).



(65)

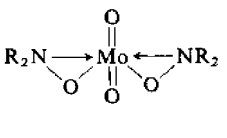
While some molybdenum complexes such as MoO_3(dien) were found to be inactive,[236] the rates of molybdenum-catalyzed epoxidation of alkenes were found to be independent of the structure of the complex used, after an induction period representing the time for exchange of anionic ligands by the alkyl hydroperoxide. *cis*-Dioxomolybdenum(VI) diolates such as (**78**) were isolated



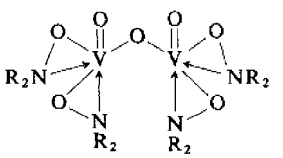
(**78**)

at the end of the reaction, and probably result from the reaction of the Mo^{VI} catalyst with the epoxide product.

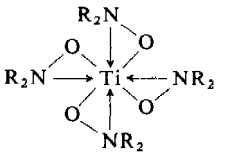
^{18}O Labeling studies have clearly shown that the active catalyst is not a peroxo compound but an alkyl peroxide in which the alkyl peroxide group is probably O,O-triangularly bonded to the metal,[121,229] as illustrated by the X-ray crystal structure of the vanadium complex (**22**).[46] The well-characterized d^0 metal *O,N*-bonded *N,N*-dialkylhydroxylamino complexes (**79**),[237,238] (**80**)[237] and (**81**)[239] might be reminiscent of the alkyl peroxide complexes of Mo^{VI}, V^V and Ti^{IV}, which are difficult to isolate and involved as reactive intermediates in reactions (64) or (65).



(**79**)

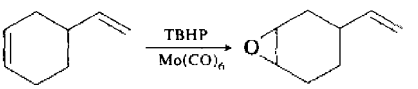


(**80**)



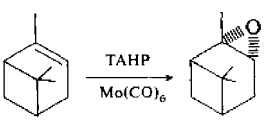
(**81**)

(*b*) *Alkenes.* The reactivity of double bonds is enhanced by increasing alkyl substitution following the order tetrasubstituted > trisubstituted > disubstituted > monosubstituted. This is illustrated by the regiospecific monoepoxidation of conjugated dienes (equation 66).[225]

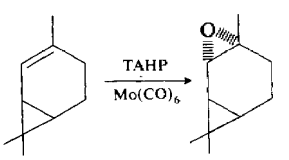


(66)

Electron withdrawing groups on the alkene considerably retard the epoxidation. For example, acrylic esters and acrylonitrile are not reactive, while allyl chloride is about one tenth as reactive as propylene towards TBHP/Mo^{VI}.[240] The epoxidation of alkenes is completely stereoselective: *cis*-alkenes are exclusively transformed into *cis*-epoxides and *trans*-alkenes into *trans*-epoxides. Oxygen addition to the double bond preferentially occurs from the less shielded face of the substrate, *e.g.* in the selective epoxidation of terpenes by *t*-pentyl hydroperoxide (*t*-amyl hydroperoxide, TAHP) (equations 67 and 68).[225]

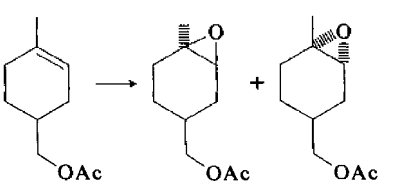


(67)



(68)

The presence of the substrate of functional groups capable of interacting with the metal directs the stereoselectivity of the epoxidation, as shown by the comparative reactivity of (**82**) towards TAHP/$Mo(CO)_6$ and peroxybenzoic acid (PBA).[241]



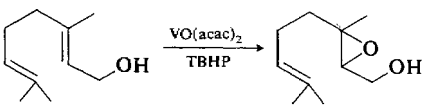
(69)

(**82**)

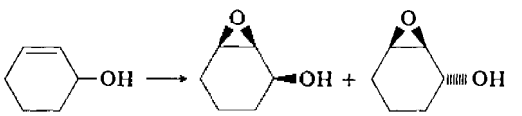
TAHP/$Mo(CO)_6$	100%	0%
PBA	50%	50%

Allylic and homoallylic alcohols are particularly good substrates for epoxidation by TBHP/V^V and TBHP/Mo^{VI} catalysts, with the former being superior in activity and selectivity (equations 70–72).[57,226,242] Allylic alcohols have also been shown to be particularly good substrates for enantioselective epoxidation. Good results were observed in some cases with TBHP/$VO(acac)_2$/chiral hydroxamates (equation 73),[57] but a major breakthrough was obtained

using TBHP/$Ti(OR)_4$ in the presence of dialkyl tartrate as the chiral ligand (equation 74). This method has proved to be very useful for the asymmetric epoxidation of a wide range of prochiral allylic alcohols with good yields and enantiometric excesses exceeding 90%.[243,244]

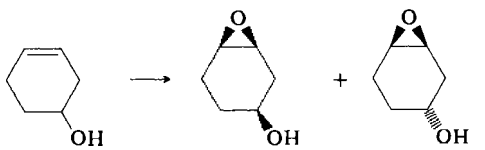


(70)



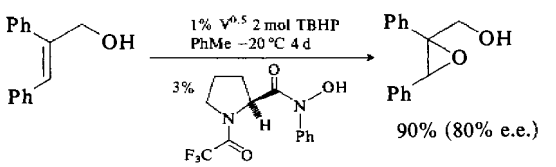
(71)

TBHP/$Mo(CO)_6$	98%	2%
TBHP/$VO(acac)_2$	98%	2%

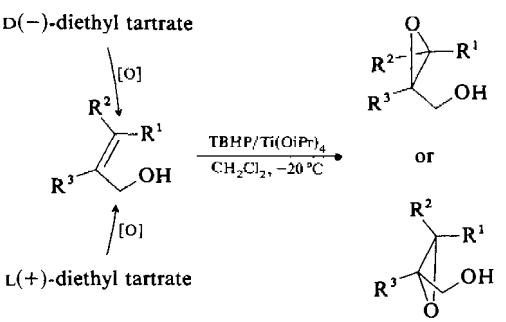


(72)

TBHP/$Mo(CO)_6$	98%	2%
TBHP/$VO(acac)_2$	98%	2%



(73)

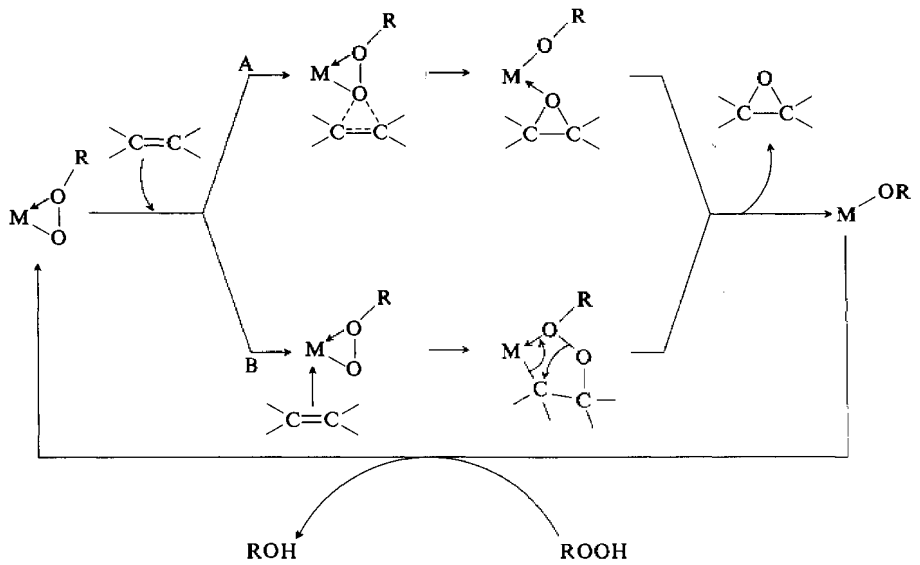


(74)

(*c*) *Effect of solvent, ligands and coproduct alcohol.* The d^0 metal-catalyzed epoxidation of alkenes requires anhydrous conditions, with the inhibiting effect of water being more pronounced for V and Ti than for Mo and W. Chlorinated (*e.g.* CH_2Cl_2, $C_2H_4Cl_2$) or aromatic solvents (*e.g.* benzene, toluene) are suitable for good catalyst activity, but alcohols or basic solvents, *e.g.* DMF, THF and dioxane, strongly retard or completely inhibit the oxidation. The coproduct alcohol derived from the hydroperoxide also exerts an inhibitory effect in the order W < Mo < Ti < V[245] and competes with the alkyl hydroperoxide by forming metal alkoxides, preventing the formation of metal-alkyl peroxides.

(*d*) *Mechanism.* It is now generally admitted that this reaction, owing to its very high selectivity and stereospecificity, proceeds according to a heterolytic rather than a homolytic mechanism. Two alternative mechanisms (A and B; Scheme 5) emerge from the numerous interpretations proposed.[56]

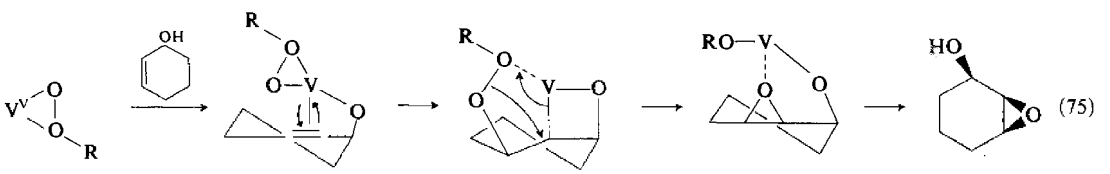
(A) Nucleophilic attack of the alkene on the 'electrophilic' oxygen atom covalently bound to the metal, which is reminiscent of Bartlett's butterfly mechanism for epoxidation of alkenes by percarboxylic acids.[229]



Scheme 5

(B) Complexation of the alkene to the metal followed by its insertion between the metal-oxygen bond according to an intramolecular 1,3-dipolar mechanism, forming a five-membered pseudocyclic peroxometallacycle which decomposes to give the epoxide and the metal alkoxide.[121,162,193,634]

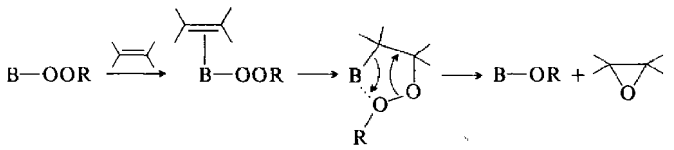
Although there is no definitive proof establishing one or the other proposal, mechanism (B) appears to explain most of the characteristics of the reaction. This mechanism is consistent with the general π-σ rearrangement procedure occurring in most heterolytic metal-catalyzed transformations of alkenes,[158] and is close to that proposed for the epoxidation of alkenes by Mo-peroxo complexes (equation 26), which has similar characteristics. As it involves a Lewis base-Lewis acid metal-alkene bond, it is consistent with the reactivity of alkenes increasing with their nucleophilic nature, and with the strong inhibition by basic ligands and solvents which compete with the alkene for vacant sites on the metal. Further, the absence of heterolytic reactivity of the dipicolinatovanadium(V)-alkyl peroxide complex (**22**), which has no available coordination sites, disfavors noncomplexation mechanism (A). Also, mechanism B, involving rigid metallacyclic intermediates, is better suited to explain the very high stereoselectivity of the reaction, *e.g.* in the case of allylic alcohols, as shown by equation (75).[121,162]



(75)

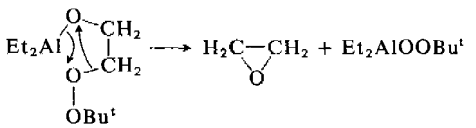
If we consider the d^0 metal-*N*,*N*-dialkylhydroxylamino complexes (**79**), (**80**) and (**81**) as valid models for the reactive but unstable alkyl peroxide species $MoO_2(OOR)_2$, $VO(OOR)_3$ or $V_2O_3(OOR)_4$, and $Ti(OOR)_4$ presumably involved in catalytic oxidations, the low activity of vanadium and titanium for the epoxidation of simple alkenes could be interpreted by the fact that these alkenes cannot displace the *O*,*O*-bonded alkyl peroxide groups in the coordinatively saturated V^V- and Ti^{IV}-alkyl peroxide species, whereas allylic alcohols can displace the alkyl peroxide groups by forming bidentate allylic alkoxides as in equation (75).[162]

Since the metal-alkene association preceding the peroxymetalation reaction in mechanism (B) is a pure Lewis acid/Lewis base interaction, it would be expected that compounds having alkylperoxy groups bonded to a Lewis acid center should be active for the epoxidation of alkenes. This is indeed found for boron compounds, which are active as catalysts for the epoxidation of alkenes by alkyl hydroperoxides.[246,247] Isolated boron tris(alkyl peroxides), $B(OOR)_3$, have been shown to epoxidize alkenes stoichiometrically, presumably through alkylperoxyboration of the double bond (equation 76).[248]



(76)

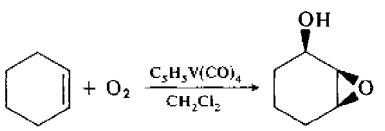
Aluminum compounds such as $Al(OBu^t)_3$ have also been shown to catalyze the selective transformation of allylic alcohols into *syn*-epoxides.[249] Related to the mechanism of this reaction is the decomposition of the aluminum compound (**83**) to give ethylene oxide.[250]



(77)

(**83**)

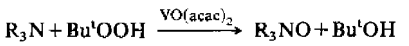
Epoxides can also be formed from the oxidation of alkenes by molecular oxygen *via in situ* generation of hydroperoxides by autoxidation.[251,252] An interesting example is the direct stereoselective oxidation of cyclohexene by O_2 to *syn*-1,2-epoxycyclohexan-3-ol catalyzed by $CpV(CO)_4$ with a 65% yield and ~99% stereoselectivity (equation 78).[253]



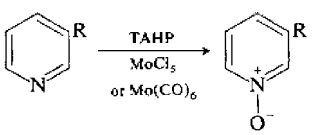
(78)

(iii) Oxidation of other substrates

Alkyl hydroperoxides can oxidize a variety of other nucleophilic substrates in the presence of d^0 metal catalysts. Thus molybdenum and vanadium catalysts have been used for the selective oxidation of tertiary amines to the corresponding *N*-oxides (equations 79 and 80).[225,254]

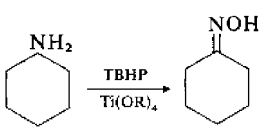


(79)



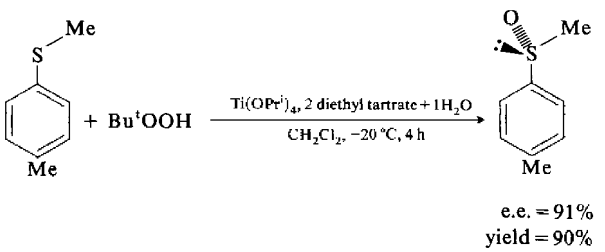
(80)

Primary amines such as cyclohexylamine are selectively converted to oximes by TBHP in the presence of Ti, V, Mo and W compounds. Titanium compounds, such as $Ti(OBu)_4$, were found to be the best catalysts (equation 81).[255]



(81)

The oxidation of sulfides to sulfoxides by TBHP in the presence of Mo and V catalysts has been extensively studied.[230,256] A modified Sharpless reagent,[243] *i.e.* $Ti(OPr^i)_4$/2 diethyl tartrate/1 H_2O, was used for the asymmetric oxidation of prochiral sulfides to sulfoxides with enantiomeric excess greater than 90% (equation 82).[160,257]



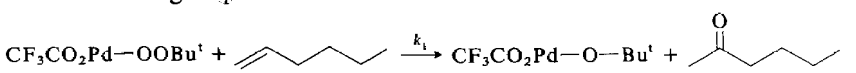
(82)

e.e. = 91%
yield = 90%

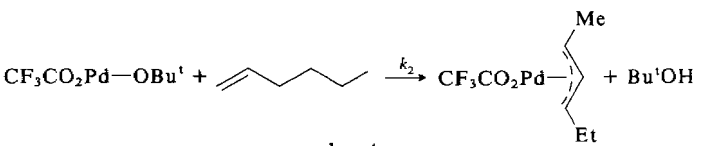
61.3.2.2.2 Group VIII metal alkylperoxo and hydroperoxo complexes

(i) Palladium catalysts

Palladium *t*-butyl peroxide carboxylates $[Pd(OOBu^t)(RCO_2)]_4$, easily prepared by reaction (9), and characterized by X-ray crystallography (formula **23**), are very effective reagents for the selective oxidation of terminal alkenes to methyl ketones under anhydrous and anaerobic conditions.[42] Their reactivity decreases in the order $R = CF_3 > CCl_3 \gg CH_3$. The reaction has been shown to proceed in two steps: (a) oxygen transfer from the *t*-butyl peroxide complex to the alkene, producing the methyl ketone and the palladium-*t*-butoxy complex (equation 83), followed by (b) a rapid substitution of the OBu^t group by the alkene on the metal, resulting in the formation of *t*-butyl alcohol and the π-allylic complex (equation 84). Only terminal alkenes are selectively converted to methyl ketones. Internal alkenes directly produce the π-allylic complex upon exchange with the $OOBu^t$ groups.



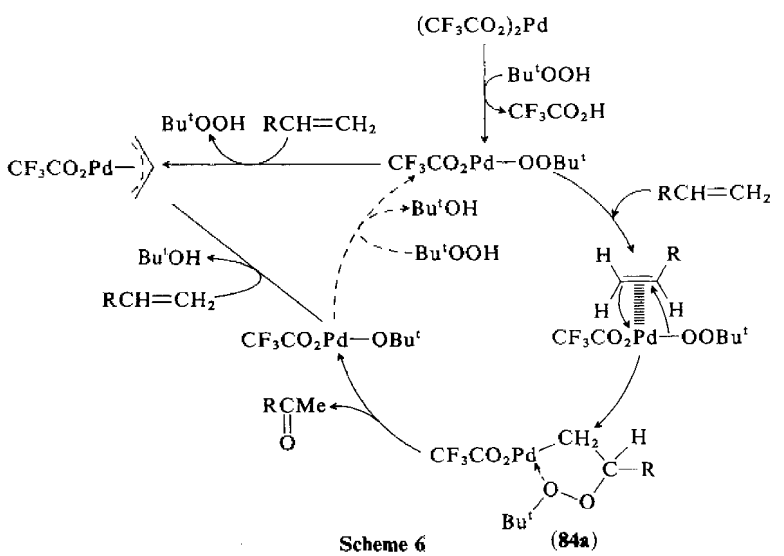
(83)



(84)

$k_2 \gg k_1$

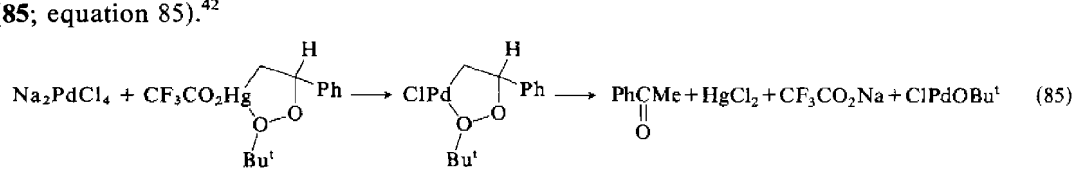
The general trends of this oxidation are consistent with the mechanism depicted in Scheme 6. This involves the complexation of the alkene to the metal followed by its insertion into the palladium-oxygen bond, forming the five-membered pseudocyclic intermediate which decomposes to give the methyl ketone and the palladium-*t*-butoxy complex. The decomposition of (**84a**) is similar to that of the rhodium dioxametallacycles previously shown in Scheme 3.[42]



Scheme 6

(**84a**)

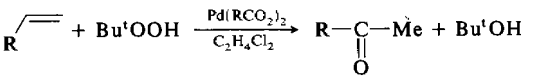
It can be seen that the pseudocyclic intermediate (**84a**) strongly resembles the stable alkylperoxy-mercury compound (**84b**) prepared from the reaction of TBHP with an alkene in the presence of mercury(II) carboxylate.[258] The X-ray structure of the similar $BrHg\{CH(Ph)CH(Ph)(OOBu^t)\}$ compound has clearly shown the pseudocyclic nature of this adduct by the interaction existing between mercury and the OBu^t group.[259] The transmetalation of mercury by palladium in (**84b**) produces acetophenone in 95% yield, presumably *via* the formation of the pseudocyclic intermediate (**85**; equation 85).[42]



(85)

(**84b**) (**85**)

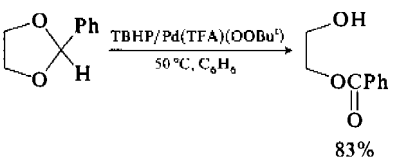
Methyl ketones can be catalytically produced when an excess of TBHP is used for regenerating the initial *t*-butyl peroxide species from the resulting alkoxy complex in Scheme 6. To prevent the formation of a π-allylic complex from causing lower selectivities, a large excess of TBHP with respect to the alkene is required (equation 86).[260]



(86)

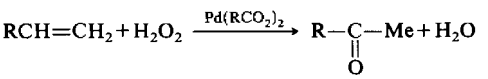
70–85%

Among palladium complexes, $[Pd(CF_3CO_2)(OOBu^t)]_4$ was found to be the best catalyst for the oxidative cleavage of cyclic acetals to monoesters of diols by TBHP (equation 87).[261] Palladium carboxylates are also effective catalysts for the selective oxidation of terminal alkenes to methyl ketones by hydrogen peroxide (equation 88).[262] This reaction occurs at room to moderate (80 °C) temperature, in a two-phase (benzene or AcOEt) or single-phase (Bu^tOH or AcOH) solution. Only terminal alkenes, *e.g.* 1-hexene, 1-octene, allyl acetate, are selectively converted to methyl ketone. ^{18}O Labeling studies showed that ketonic oxygen is derived from hydrogen peroxide, and not water as in the Wacker process. The suggested mechanism is similar to that of the ketonization of alkenes by $PdOOBu^t$ complexes, and involves palladium hydroperoxide as the reactive intermediate (equation 89).[262]



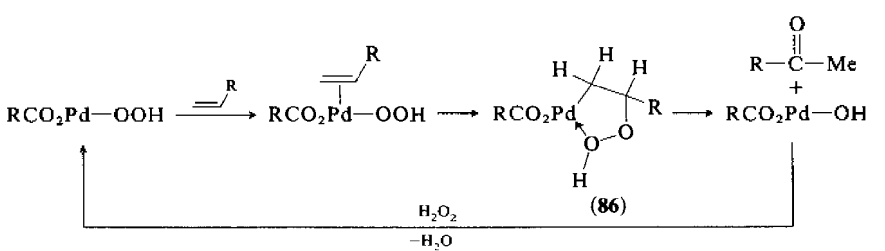
(87)

83%



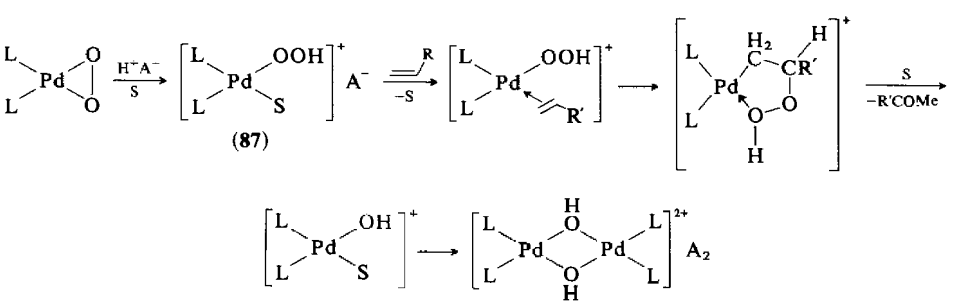
(88)

70–90%



(89)

Evidence for the pseudocyclic intermediate (**86**) was obtained by the formation of acetophenone in 85% yield upon reaction of Li_2PdCl_4 with $CF_3CO_2HgCH_2CH(Ph)OOH$, as in reaction (85).[263] Treatment of nonreactive $PdO_2(PPh_3)_2$ with one equivalent of $MeSO_3H$ results in the formation of a coordinatively unsaturated hydroperoxide complex which reacts with terminal alkenes to give the corresponding methyl ketone. ^{18}O Labeling studies showed that the ketonic oxygen atom is derived from molecular oxygen, not water.[263] Using CF_3CO_2H instead of $MeSO_3H$ results in the formation of an inactive hydroperoxo complex due to the occupation of the vacant site S in (**87**) by the trifluoroaceto group, impeding coordination of the alkene (equation 90).[263] α,β-

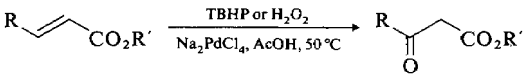


(87)

(90)

12044 L = PPh_3; S = CH_2Cl_2; A = $MeSO_3^-$, BF_4^-

Unsaturated esters or α,β-unsaturated ketones are efficiently oxidized to β-keto esters and β-diketones by TBHP or H_2O_2 in the presence of Na_2PdCl_4 (equation 91). The oxidation of terminal alkenes under these conditions results in extensive double bond migration and lower selectivities.[264]



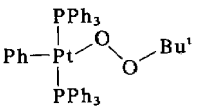
(91)

(ii) Platinum catalysts

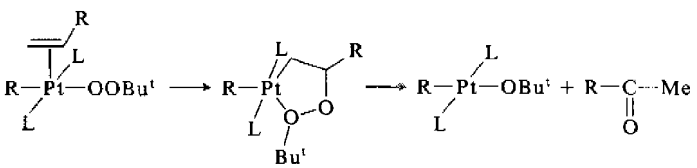
Platinum-alkylperoxo and -hydroperoxo complexes are much less effective ketonization reagents than their palladium analogs. The platinum-hydroperoxide complex generated by protonation of $Pt(PPh_3)_2O_2$ as in equation (90) was found to be inactive,[133] as well as $Pt(CF_3)(OOH)(depe)$ obtained from the reaction of H_2O_2 with the corresponding hydroxo complex.[265]

However, the platinum-*t*-butyl peroxide complex $[Pt(CF_3CO_2)_2(OOBu^t)(Bu^tOH)]_2$ selectively transforms terminal alkenes (*e.g.* 1-octene) into the corresponding methyl ketone,[220] but much less efficiently than the palladium complex (**23**).[42] This reaction becomes slightly catalytic in the presence of excess TBHP.

Strukul and coworkers recently prepared a series of *cis* and *trans* isomers of the platinum-*t*-butyl peroxide complexes $Pt(R)(OOBu^t)L_2$ (R = CF_3, Ph, *etc.*; L = tertiary phosphine). The X-ray crystal structure of the *trans*-$[Pt(Ph)(OOBu^t)(PPh_3)_2]$ (**88**) revealed a square-planar arrangement with end-bonded $OOBu^t$ group.[219] Interestingly, only the *trans* isomers were found to be capable of oxidizing terminal alkenes to methyl ketones, whereas the *cis* isomers were inactive. The suggested mechanism involves the coordination of the alkene leading to a five-coordinate intermediate, followed by a pseudocyclic peroxymetalation, as in Scheme 6 (equation 92).[219]



(**88**)

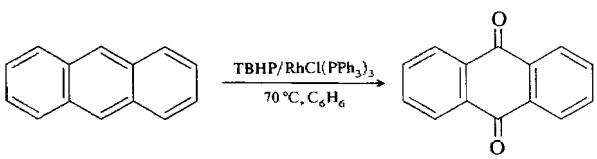


(92)

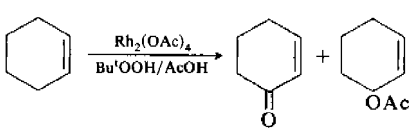
(iii) Rhodium and iridium catalysts

Although no direct oxygen transfer reactions from well-characterized rhodium-hydroperoxo or -alkylperoxo complexes to alkenes have yet been reported, these species are probably involved in the rhodium-copper catalyzed ketonization of terminal alkenes by O_2, as previously shown in Section 61.3.2.1.3. Rhodium trichloride has been used to catalyze the ketonization of terminal alkenes by H_2O_2 or TBHP in alcoholic solvents, but these reactions occur less efficiently than with the $Rh/Cu/O_2$ system.[207]

Anthraquinone was produced in 96% yield from the oxidation of anthracene with TBHP in the presence of $RhCl(PPh_3)_3$ catalyst (equation 93).[266] Oxidation of cylic alkenes, *e.g.* cyclopentene, cyclohexene, cycloheptene, by TBHP in the presence of $Rh_2(OAc)_4$ results in the formation of α,β-unsaturated ketones and allylic acetates as the major products (equation 94).[267]



(93)



(94)

In contrast to inactive iridium(III)-Peroxo complexes, Ir^{III}-hydroperoxo species have been shown to transfer oxygen to a coordinated alkene, for example in the slightly catalytic oxidation of cyclooctene to cyclooctanone by O_2+H_2 mixtures in the presence of $IrHCl_2(C_8H_{12})$ (equation 95).[268] Oxygen transfer presumably occurs as for palladium hydroperoxides in equations (89) and (90).

$$IrHCl_2(C_8H_{12}) \xrightarrow[DMA]{O_2} Ir(OOH)Cl_2(C_8H_{12}) \longrightarrow Ir(OH)Cl_2 + C_8H_{12}O \qquad (95)$$

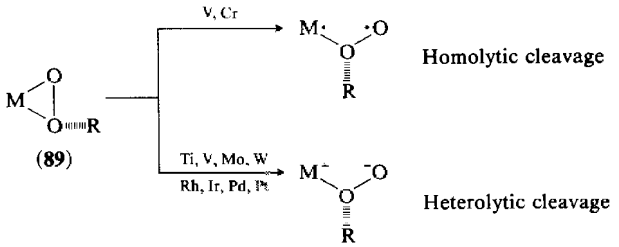
$$\uparrow \quad \xleftarrow[-H_2O]{H_2+C_8H_{12}} \quad \downarrow$$

A similar ketonization of coordinated cyclooctene was observed in the reaction of $[Ir(C_8H_{12})_4]^+BF_4^-$ with O_2 in the presence of one equivalent of fluoroboric acid, and probably occurs *via* Ir—OOH species according to a similar mechanism.[133]

As previously shown for platinum *versus* palladium complexes, iridium complexes are generally much less effective catalysts than rhodium ones for the ketonization of alkenes by O_2, H_2O_2 or ROOH.

61.3.2.3 Conclusion

The catalytic properties of transition metal complexes in the reactions considered above are related to the existence and reactivity of their peroxide derivatives. For d^0 metals the general characteristics of the oxidations and the resulting oxygenated products are similar using hydrogen peroxide or alkyl hydroperoxides, although the nature of the active species, peroxo or alkylperoxo, is different. The same is true for Group VIII metals for which the ketonization of alkenes occurs using O_2, H_2O_2 or ROOH as the oxygen source, and involves different peroxide species. One likely rationale is to consider that the active peroxo, alkylperoxo or hydroperoxo species reacts in the triangular form (**89**). This has been shown to be the case for d^0 metal peroxides, but not for Group VIII metal alkyl- or hydro-peroxides which, in the solid state, have an end-on linear or bridged structure. However, the recent preparation of η^2-SSR complexes, *e.g.* $[Ir(\eta^2\text{-}S_2Me)(dppe)_2]^{2+}$[268a,b] and $[Os(\eta^2\text{-}S_2Me)(CO)_2(PPh_3)_2]^+$,[268c] which are the sulfur analogues of η^2-OOR complexes, could suggest that such *O,O*-bonded alkyl peroxide species might also exist in solution. A further rationale is that the heterolytic or homolytic nature of the catalytic oxidation seems to be strongly governed by the heterolytic or homolytic dissociation mode of the peroxide moiety, which depends on the nature of the metal (Scheme 7).



Scheme 7

Heterolytic oxidations require releasable coordination sites on the metal, involve strained metallocyclic intermediates and are highly selective. By contrast, homolytic oxidations involve bimolecular radical processes with no metal-substrate association and are less selective.

61.3.3 METAL–OXO COMPLEXES IN OXIDATION

The use of high-valent metal-oxo compounds as stoichiometric oxidizing reagents of organic substrates has been known for over a century. Table 5 lists some of the most representative examples of such compounds, together with their structural characteristics and their reactivity. A majority of metal-oxo reagents, *viz.* CrO_2Cl_2, MnO_4^-, FeO_4^{2-}, RuO_4 and OsO_4, involve the metal in its higher oxidation state with a d^0 configuration and a tetrahedral structure.[50]

In contrast to catalytic oxidations involving metal peroxide intermediates, catalysis by metal-oxo complexes does not in theory require the presence of a coreducing agent. Indeed, the reduction

Table 5 Reactivity of Metal-Oxo Complexes

Oxo complex	*Structure*[a]	d(M=O) (Å)	ν(M=O) (cm^{-1})	*Reoxidizing agent for catalysis*	*Reactivity and/or refs.*[c]
VO_2(pic)(HMPA)	TB	1.6	935, 948	—	NR[22]
$Cr^{VI}O_2Cl_2$	TH	1.57	984	—	SE[269], HA[270,271], OA[270,272]
$Cr^{VI}O_2(OH)_2$	TH	—	—	—	HA[270], OA[270]
$Cr^{VI}O_3(py)_2$	—	—	—	—	OA[273,274]
$Cr^{VI}O_3Cl^-$	TH	1.53	907, 954	—	OA[275,276]
$Cr^{VI}O_2(NO_3)_2$	—	—	—	—	SE[277]
$Cr^{V}O$(salen)$^+$	SP	1.49	997	PhIO	SE[278]
$Mo^{VI}O_2Cl_2(DMF)_2$	OH	1.68	905, 940	—	NR[279]
$Mo^{VI}O_2(Et_2dtc)_2$	OH	1.63	908, 877	O_2(for PR_3)	PO[280,281]
$Mn^{VII}O_4^-$	TH	1.62	838, 921[b]	—	282, HA, OC[283,284]
$Re^{VII}{}_2O_7$	—	1.65, 1.74	1009	H_2O_2	E, K[285]
$Fe^{VI}O_4^{2-}$	TH	—	778, 800[b]	—	HA, [54]OA[286,287]
$Ru^{VIII}O_4$	TH	1.70	883, 918[b]	ClO^-, PhIO, IO_4^-, $S_2O_8^{2-}$, R_3NO	OC, OA[288,289]
$Os^{VIII}O_4$	TH	1.697	964, 953[b]	H_2O_2, TBHP, ClO^- ClO_3	DO[57,290]
$Se^{IV}O_2$	—	1.78	924	TBHP	AO[291-293]

[a] Abbreviations: Et_2dtc = diethyl dithiocarbamate; TB = trigonal-bipyramidal; TH = tetrahedral; SP = square-pyramidal; OH = octahedral.
[b] $\nu1(A_1)$ and $\nu3(F_3)$ absorptions, data taken from ref. 50.
[c] NR = not reactive toward hydrocarbons; SE = stereoselective epoxidation; E = epoxidation; HA = hydroxylation of alkanes; OA = oxidation of alcohols to carbonyl compounds; PO = oxidation of phosphines to phosphine oxides; OC = oxidative cleavage of alkenes; K = ketonization of alkenes; DO = hydroxylation of alkenes to diols; AO = allylic oxidation of alkenes.

of the oxo metal by a substrate could directly produce the reduced complex, which can be reoxidized by dioxygen to the initial oxo complex. In fact, with one notable exception (the catalytic oxidation of phosphines by O_2 in the presence of dioxodithiocarbamatemolybdenum(VI) complexes), the reduced species of metal-oxo reagents cannot be reoxidized by air, but require stronger oxidants such as ClO^-, PhIO, IO_4^-, $S_2O_8^{2-}$, *etc.*, and in some cases H_2O_2 or TBHP (Os, Se).

61.3.3.1 Chromium

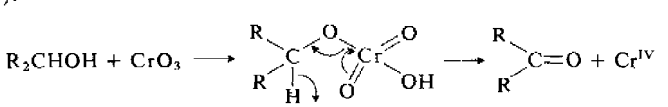
The oxidative properties of chromium-oxo complexes towards organic substrates have been thoroughly investigated, and several reviews have appeared in recent years.[270-276] We will only briefly consider the oxidation of alcohols to carbonyl compounds, the epoxidation of alkenes and the hydroxylation of hydrocarbons.

61.3.3.1.1 Oxidation of alcohols to carbonyl compounds

A variety of chromium(VI)-oxo reagents, *e.g.* chromic acid, dichromate ion, $CrO_3(py)_2$, CrO_3(Bipy), CrO_2Cl_2, $CrO_2(OAc)_2$, $CrO_2(OBu^t)_2$, $CrO_3Cl^-pyH^+$, have been extensively used by organic chemists in both soluble and supported forms for the selective oxidation of alcohols.[270-276,294] Under optimal conditions, 1.5 equivalents of carbonyl compounds are produced per mole of chromium(VI)-oxo reagent (equation 96).

$$3R_2CHOH + CrO_3 + 6H^+ \rightarrow 3R_2C{=}O + 2Cr^{III} + 6H_2O \quad (96)$$

It is now generally admitted that this reaction involves both one-electron and two-electron transfer reactions. Carbonyl compounds are directly produced from the two-electron oxidation of alcohols by both Cr^{VI}- and Cr^{V}-oxo species, respectively transformed into Cr^{IV} and Cr^{III} species. Chromium(IV) species generate radicals by one-electron oxidation of alcohols and are responsible for the formation of cleavage by-products, *e.g.* benzyl alcohol and benzaldehyde from the oxidation of 1,2-diphenylethanol.[294,295] The key step for carbonyl compound formation is the decomposition of the chromate ester resulting from the reaction of the alcohol with the Cr^{VI}-oxo reagent (equation 97).[296]

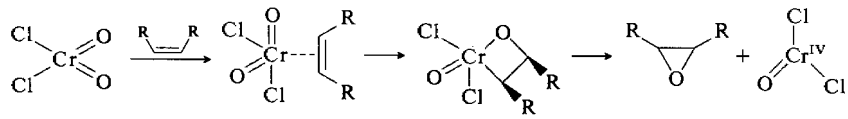


(97)

The most widely used chromium(VI)-oxo reagents for synthetic use in organic chemistry are the Collins reagent, $CrO_3(py)_2$,[273] and the Corey reagent, $CrO_3Cl^-pyH^+$,[297] with the latter being superior for the oxidation of primary alcohols to aldehydes.[275]

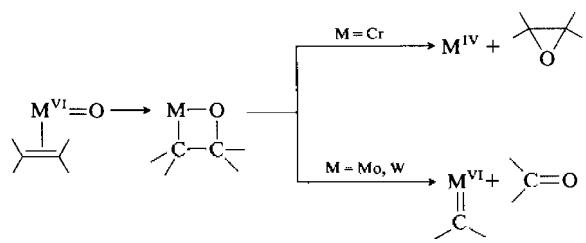
61.3.3.1.2 Epoxidation of alkenes

Chromium(VI)-oxo compounds are generally poor reagents for the selective transformation of alkenes to epoxides and give a complex mixture of products.[277] However, the reaction of CrO_2Cl_2 with *cis*-alkenes at low temperature was found to give mainly *cis*-epoxides, as well as chlorohydrin and vicinal dichloride arising from *cis* addition processes. These results were interpreted by Sharpless by a mechanism involving an initial alkene-chromium(VI) π-complex which rearranges to an oxametallacyclobutane intermediate which decomposes to give the epoxide with high retention of configuration (equation 98).[269]



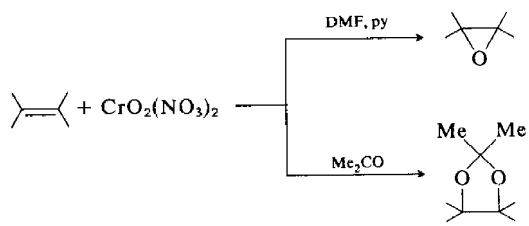
(98)

Ab initio theoretical methods showed that oxametallacyclobutane formation was indeed the most favored route for the reaction of chromyl chloride with ethylene.[298] Whereas the chromium metallacycle preferentially decomposes to epoxide by reductive elimination, calculations predict that the molybdenum and tungsten analogs would preferentially undergo carbon-carbon bond cleavage leading to metal-carbene species and carbonyl products arising from oxidative cleavage of the double bond (equation 99). However, MoO_2Cl_2 and WO_2Cl_2 complexes have been found to date to be quite reluctant to react with alkenes at moderate temperatures.[123]



(99)

Chromyl nitrate, $CrO_2(NO_3)_2$, was found by Miyaura and Kochi to be a much better epoxidizing reagent than CrO_2Cl_2.[277] This reaction is solvent dependent. In basic solvents such as DMF or pyridine, epoxide is the major product (equation 100), whereas in an acetone solution alkene ketal, resulting from the addition of acetone to epoxide, is predominantly produced (equation 101).

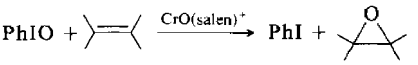


(100)

(101)

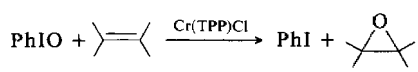
The epoxidation of alkenes in DMF occurs with a high retention of configuration. Both *cis*- and *trans*-β-methylstyrene are stereospecifically converted to the corresponding *cis*- and *trans*-epoxides, respectively, in high yield. The reactivity of alkenes follows the order norbornene > α-methylstyrene > β-methylstyrene > styrene > cyclohexene $\gg$ 1-octene. ESR experiments showed that the actual oxidizing species are oxochromium(V) compounds formed by one-electron oxidation of solvent. In further support of this finding, Kochi and coworkers isolated, and characterized by X-ray crystallography, the chromium(V)-oxo complex $CrO(salen)^+PF_6^-$ (**90a**) obtained by treatment of $Cr(Salen)(H_2O)_2^+PF_6^-$ with iodosylbenzene.[278] This complex (**90a**) is an effective stoichiometric reagent for the selective epoxidation of alkenes, and can be used to catalyze the epoxidation of alkenes by iodosylbenzene (equation 102). The reactivity of various alkenes with

this catalytic system is similar to that previously observed in stoichiometric epoxidation by chromyl nitrate.



(102)

The catalytic epoxidation of equation (102) is similar to that previously found by Groves and coworkers using chromium(III) tetraphenylporphyrin as catalyst (equation 103).[299] These authors convincingly demonstrated, by means of IR, ESR and ^{18}O-labeling experiments, that the active species of reaction (103) is an oxoporphinatochromium(V) complex, CrO(TPP)Cl (**90b**), presumably with a structure similar to (**90a**). One question raised by the reactivity of (**90a**) and (**90b**), which have no suitable coordination site, is whether the alkene is coordinated to the metal before oxametallacyclobutane formation as in the previous Sharpless proposal of equation (98). Groves suggested that the attack of the double bond occurs from the side and parallel to the plane of the porphyrin, which corresponds to a maximum overlap between the π-orbitals of the approaching alkene and those of the singly occupied π-antibonding orbitals of the metal-oxo group.[300]



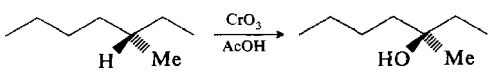
(103)

61.3.3.1.3 Hydroxylation of hydrocarbons

The oxidation of toluene to benzoic acid by CrO_2Cl_2 in acetic acid was described by Carstanjen more than 100 years ago.[301] Shortly thereafter, Etard isolated an organometallic complex with the formula $PhMe{\cdot}2CrO_2Cl_2$ from the reaction of CrO_2Cl_2 with toluene.[302] This complex gave benzaldehyde in high yield upon treatment with water. A similar complex from triphenylmethane gave triphenyl methanol on hydrolysis.[271] Unfortunately, X-ray structural analyses of these complexes are still lacking and would greatly help in understanding the mechanism of hydrocarbon hydroxylation by chromium–oxo reagents.

The main characteristics of the oxidation of hydrocarbons by chromic acid and chromyl compounds are as follows.[270,54]

(1) Alkanes are preferentially hydroxylated at the more nucleophilic C—H bonds, with relative reactivities tertiary : secondary : primary hydrogens = 7000 : 110 : 1.[303] This reaction occurs with a high retention of configuration at the hydroxylated carbon atom, as shown by the selective formation of *cis*-9-decalol from the oxidation of *cis*-decalin with chromyl acetate in an acidic medium[304] and the hydroxylation of chiral (+)-3-methylheptane (**91**) to chiral alcohol (**92**) with 72 to 85% retention of configuration.[305]

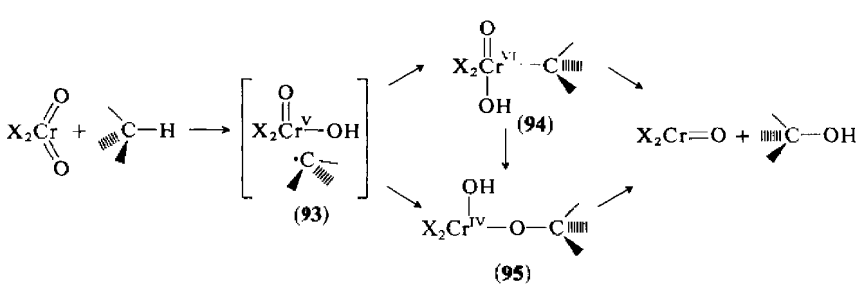


(**91**) (**92**) (104)

(2) Toluene and its substituted derivatives are oxidized by sodium dichromate or chromyl chloride mainly into the corresponding benzoic acids or benzaldehydes in good yields.[270] No or very little ring hydroxylation is observed.

(3) Polynuclear aromatic compounds such as naphthalene or anthracene are oxidized by chromyl reagents mainly into quinones, with a significant NIH shift, providing evidence for the intermediacy of arene oxide intermediates.[306,54]

Among the various proposals for the hydroxylation of C—H bonds by chromyl reagents, the mechanism involving a hydrogen atom abstraction by the oxo reagent giving a chromium(V)-carbon free radical cage structure (**93**), followed by a rapid collapse to give the alkyl-chromium(VI)



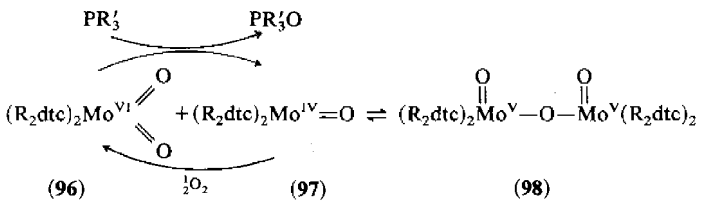
(105)

intermediate (**94**) or the Cr^{IV} ester (**95**), which decomposes to alcohol and Cr^{IV}, satisfactorily accounts for most of the data concerning this reaction.

61.3.3.2 Molybdenum and Tungsten

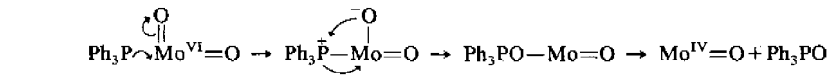
Trioxo and *cis*-dioxo complexes of molybdenum(VI) and tungsten(VI) are more stable and therefore much less reactive than their chromium analogs. However, the use of strongly donating sulfur chelate ligands such as dialkyl dithiocarbamate (R_2dtc)[280] results in the labilization of the Mo=O bonds in the complexes $MoO_2(R_2dtc)_2$, as shown by the decrease in the IR frequencies of the Mo=O stretching vibrations in comparison with other Mo^{VI}-*cis*-dioxo complexes.[307]

Barral and Bocard showed that the complexes $MoO_2(R_2dtc)_2$ (R = Et, Pr^n, Bu^i) catalyze the oxidation of phosphines to phosphine oxides at room temperature and atmospheric oxygen pressures.[280] The steps of this catalytic reaction have been studied individually. The molybdenum-dioxo complex (**96**) reacts with PPh_3 in an inert atmosphere to give Ph_3PO and the isolated Mo^{IV}-monooxo complex (**97**), and this reduced complex (**97**) reacts readily with dioxygen to regenerate the active dioxo complex (**96**). This catalytic oxidation is complicated by a disproportionation between (**96**) and (**97**) giving a dinuclear Mo^{V} species (**98**; equation 106).[280]



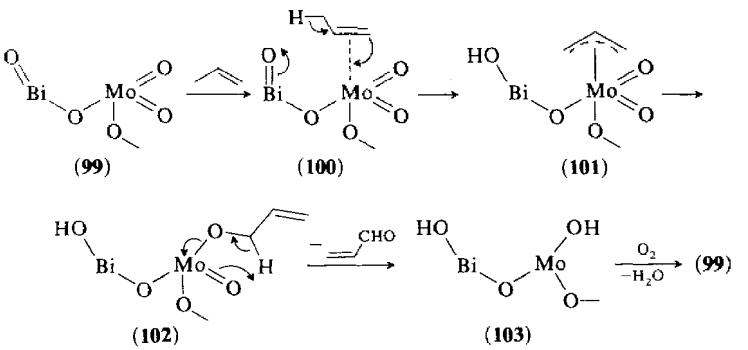
(106)

Since this reaction is inhibited by the presence of strongly complexing diphosphines, it seems likely that oxidation proceeds through the prior complexation of the phosphine to the metal followed by the transfer of an oxo oxygen atom to the coordinated phosphine (equation 107).[12] These complexes (**96**) also oxidize hydrazobenzene to azobenzene,[307] but are weak oxidants and do not react with alkenes.[56]



(107)

Molybdenum(VI)-oxo complexes intervene as reactive species in the selective allylic oxidation of propene to acrolein in the gas phase over bismuth molybdate catalysts at high temperatures (>300 °C).[56,308-310] In industrial processes, selectivities in acrolein reaching 90% can be obtained using multicomponent catalysts based on Bi_2O_3-MoO_3.[308] It is now understood that this reaction proceeds *via* the initial formation of a symmetric allylic intermediate. Grasselli has proposed that the role of bismuth oxide is to perform the rate-determining α-hydrogen abstraction step in a Bi-Mo dinuclear species (**100**) to give a π-allyl complex (**101**). Oxygen insertion into the metal-carbon bond followed by decompostion of (**102**) results in the formation of acrolein and reduced dinuclear species (**103**).[308,309]



(108)

A somewhat similar mechanism involving Mo^{VI}-imino species (Mo=NH) resulting from the reaction of ammonia with Mo=O bonds has been suggested for the industrially important ammoxidation of propene to acrylonitrile (equation 109).[308]

$$CH_2{=}CHMe + NH_3 + \tfrac{3}{2}O_2 \xrightarrow{Bi_2O_3/MoO_3} CH_2{=}CHCN + 3H_2O \quad (109)$$

Bismuth molybdate catalysts can also cause other allylic oxidations such as the conversion of 2-methylpropene to methacrolein and α-methylstyrene to atropaldehyde, and ammoxidations such as the conversion of 2-methylpropene to methacrylonitrile and α-methylstyrene to atroponitrile.[309]

61.3.3.3 Manganese and Rhenium

61.3.3.3.1 Oxidations by permanganate

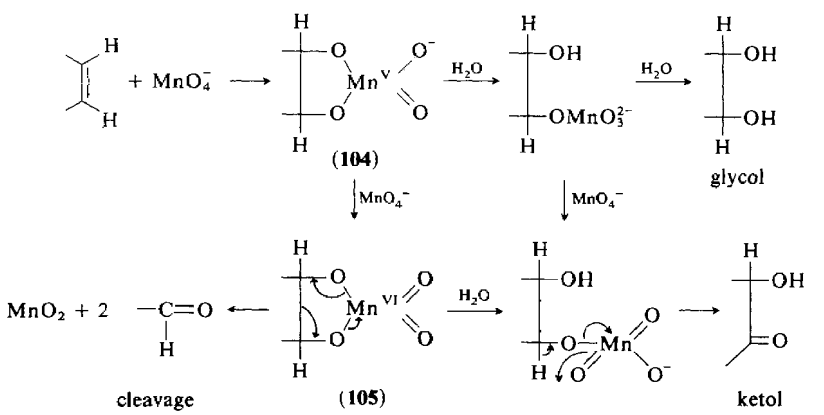
The permanganate ion MnO_4^- has been widely used by organic chemists for its strong oxidizing properties towards organic substrates.[284,311-313] The low solubility of permanganate in organic solvents requires the use of oxidation-resistant cosolvents such as acetic acid, acetone or *t*-butyl alcohol. Recent improvements consist of the use of crown ethers[314] or tetraalkylammonium and arsonium salts,[315,316] for solubilizing permanganate in inert solvents such as CH_2Cl_2 or benzene. Impregnation on inorganic supports such as molecular sieves or silica gel also activates permanganate for reaction in organic solvents.[317] The reactivity of permanganate is pH dependent and is generally enhanced in basic conditions. Manganese dioxide is usually obtained as a brown precipitate at the end of the oxidations. The main characteristics of permanganate oxidation are described below.

(i) Alcohols

Primary and secondary alcohols are readily oxidized by permanganate while tertiary alcohols are stable.[284,311] Primary alcohols are transformed into carboxylic acid *via* the formation of aldehydes. Secondary alcohols are cleanly oxidized to ketones.[294]

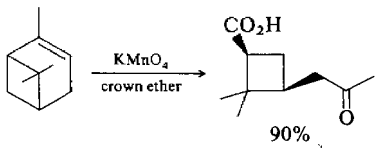
(ii) Alkenes

Decoloration of a permanganate solution (Baeyer test) is a standard procedure for detecting unsaturation in organic compounds. Oxidation of alkenes by aqueous permanganate generally results in the formation of *cis*-1,2-glycols, α-hydroxycarbonyl compounds and oxidative cleavage products. It is generally accepted that cyclic manganese(V) esters (**104**) are formed in the initial step of the reaction (Scheme 8)[184,318] as well as in the oxidation of alkenes by RuO_4 and OsO_4 (*vide infra*). *cis*-Glycols result from hydrolysis of (**104**), while cleavage products and ketols are presumably derived from a cyclic Mn^{VI} ester (**105**) resulting from the oxidation of (**104**) by the permanganate.



Scheme 8

Some synthetically useful oxidations of alkenes by permanganate can be performed under controlled conditions. For example, 1-decene could be oxidized to nonanoic acid in 91% yield by permanganate in the presence of the phase-transfer agent Aliquat 336.[319] In a benzene solution with crown ether and permanganate, α-pinene is oxidized to *cis*-pinonic acid in 90% yield (equation 110).[314]



(110)

(iii) Alkanes

Permanganate is a strong oxidant capable of hydroxylating alkanes under relatively mild conditions at the more nucleophilic C—H bonds in the order tertiary > secondary > primary. Hydroxylation of tertiary C—H bonds occurs with retention of configuration, as shown by the selective formation of *cis*-9-decalol from the oxidation of *cis*-decalin with benzyltriethylammonium permanganate.[316] Oxidation of secondary methylene groups by permanganate gives the corresponding ketone, as in the oxidation of 2-benzylpyridine to 2-benzoylpyridine (80% yield).[320]

Methyl-substituted aromatic hydrocarbons are readily oxidized by permanganate into benzoic acid derivatives.[311] Toluene, *p*-xylene and mesitylene are respectively converted to benzoic, terephthalic and trimesic acids in *ca.* 90% yield by potassium permanganate in the presence of cetyltrimethylammonium chloride.[321]

61.3.3.3.2 Oxidation by manganese dioxide

Freshly prepared MnO_2 is a useful reagent in organic chemistry and has been used in a large variety of oxidative transformations.[311] These reactions involve the allylic oxidation of alkene to α,β-unsaturated carbonyl compounds, the transformation of methylarenes to benzaldehyde and benzoic acid derivatives, the oxidation of secondary methylene groups to ketones, and the oxidation of alcohols to carbonyl compounds.[311] The yields are generally fair to good.

Manganese(V)-oxo-porphyrinato complexes have been presumed to be the active species in the epoxidation of alkenes by iodosylbenzene or hypochlorite catalyzed by manganese(III) porphyrins. This and related oxidations will be examined in more detail in Section 61.3.6.2.2.

61.3.3.3.3 Oxidation by rhenium–oxo species

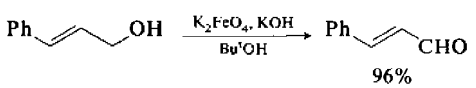
Although high-valent rhenium-oxo complexes such as perrhenate, Re_2O_7, and ReO_3X (X = F, Cl, Br) are widely known,[322] their use as oxidants is rather rare. The stoichiometric oxidation of alkenes to a mixture of ketone and epoxide by Re_2O_7 has been reported in the patent literature.[285] For example, 2-butene is transformed to 2,3-epoxybutane and 2-butanone by Re_2O_7 at 100 °C. A catalytic oxidation was observed in the presence of excess hydrogen peroxide[285] but precise data on this reaction are lacking.

61.3.3.4 Iron, Ruthenium and Osmium

61.3.3.4.1 Oxidation by ferrate ions

The only relatively stable high-valent iron-oxo complexes reported to date are ferrate(VI, V, IV) ions, *i.e.* FeO_4^{2-}, FeO_3^{3-} and FeO_4^{4-}.[323] There is considerable interest in knowing the reactivity of high-valent iron-oxo compounds, owing to the current opinion favoring their involvement as active species in biological oxygenases. Unfortunately, rather little about the chemistry of such compounds has been reported.

Potassium ferrate, K_2FeO_4, is isomorphous with chromates and readily oxidizes alcohols to carbonyl compounds in the presence of alkali.[286,287] The purple color of ferrate ion fades with the progress of the reaction. Yields as high as 96% have been reported for the oxidation of cinnamyl alcohol to cinnamaldehyde (equation 111).[287]



(111)

Barium ferrate suspended in glacial acetic acid oxidizes squalene to monoepoxysqualene in low yield.[306] Potassium ferrate is unreactive towards alkanes, but when reduced by oxalic acid it

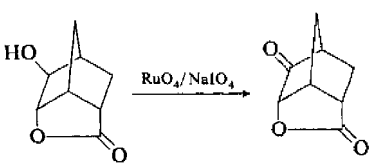
produces a presumed Fe^{IV}-oxo species capable of hydroxylating adamantane to 1-adamantanol and 2-adamantanone.[54]

61.3.3.4.2 Oxidation by ruthenium–oxo compounds

Ruthenium tetroxide, RuO_4, is a powerful oxidant, soluble in organic solvents, which was introduced by Djerassi in 1953 for applications in organic synthesis.[324] It is easily prepared by the oxidation of low-valent ruthenium compounds, *e.g.* $RuCl_3$ or RuO_2, by strong oxidants such as periodate, hypochlorite, chromic acid, *etc.*, and can be conveniently extracted from aqueous solutions into carbon tetrachloride.[288] Although RuO_4 is a strong stoichiometric oxidant by itself, modern improved procedures use only catalytic amounts of ruthenium precursors along with a suitable oxygen source such as hypochlorite, periodate, persulfate, iodosylbenzene or tertiary amine *N*-oxide.[289]

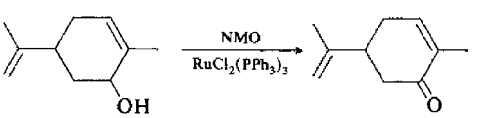
(i) Oxidation of alcohols to carbonyl compounds

Ruthenium tetroxide readily converts secondary alcohols to the corresponding ketone, and primary alcohols to aldehydes and acids.[288,294] It is particularly recommended for converting alcohols which are difficult to oxidize with other reagents, for example, the hydroxylactone (**105a**) in equation (112).[325]



(**105a**) 80% (112)

Highly selective ruthenium-catalyzed oxidation of alcohols can be achieved using low-valent complexes and milder cooxidants. For example, oxidation of primary alcohols can be cleanly stopped at the aldehyde stage by using $RuCl_2(PPh_3)_3$ as a catalyst and iodosylbenzene diacetate[326] or *N*-methylmorpholine *N*-oxide (NMO)[327] as the oxygen source. The latter system oxidizes only hydroxyl groups and preserves double bonds, as shown by the oxidation of (+)-carveol (equation 113).[327]

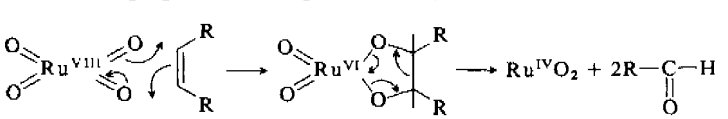


94% (113)

Ruthenium complexes such as $RuCl_3$,[328] $RuCl_3+Cu(ClO_4)_2$[329] and $RuCl_2(PPh_3)_3$[330] have been shown to catalyze the direct oxidation of alcohols to carbonyl compounds by molecular oxygen. Allylic alcohols are cleanly oxidized to the corresponding α,β-unsaturated carbonyl compounds. For example, (+)-carveol is selectively oxidized by air to (+)-carvone (92% yield) at room temperature in $C_2H_4Cl_2$ in the presence of catalytic amounts of $RuCl_2(PPh_3)_3$.[330] This reaction presumably involves the formation of a Ru^{IV} alkoxide, which undergoes β-elimination to produce the carbonyl compound and a ruthenium hydride which could be reoxidized by molecular oxygen.[330]

(ii) Oxidative cleavage of alkenes

Ruthenium tetroxide is a four-electron oxidant which directly transforms alkenic compounds into oxidative cleavage products, *i.e.* carbonyl compounds and carboxylic acids.[288] The reaction can be visualized as proceeding according to a [4+2] cycloaddition of the *cis*-dioxo moiety with the alkene, resulting in the formation of a Ru^{VI} cyclic diester which decomposes to ruthenium(IV) dioxide and oxidative cleavage products (equation 114).[288] This reaction can be made catalytic

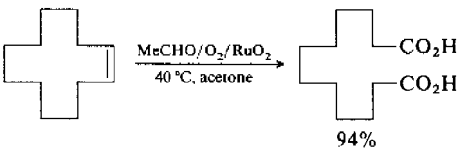


(114)

using small amounts of RuO_4, $RuCl_3$ or RuO_2 in conjunction with NaOCl (equation 115),[331] $NaIO_4$ (equation 116)[332] or peracetic acid ($MeCHO+O_2$, equation 117)[333] as cooxidant.

$$Me(CH_2)_7CH{=}CH(CH_2)_7CO_2H \xrightarrow{NaOCl/RuO_4} \underset{94\%}{Me(CH_2)_7CO_2H} + \underset{94\%}{HO_2C(CH_2)_7CO_2H} \quad (115)$$

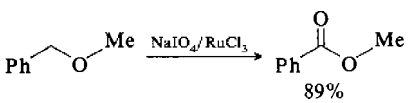
$$Me(CH_2)_3CH{=}CH(CH_2)_3Me \xrightarrow[CCl_4/MeCN]{NaIO_4/RuCl_3} \underset{88\%}{2Me(CH_2)_3CO_2H} \quad (116)$$



94% (117)

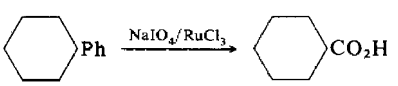
(iii) Miscellaneous oxidations

One of the most remarkable reactions performed by ruthenium-oxo complexes is the selective oxidation of aliphatic and cyclic ethers to the corresponding esters and lactones, respectively, with high yields under mild conditions.[288,334] For example, tetrahydrofuran is oxidized by RuO_4 to γ-butyrolactone with nearly quantitative yields.[334] A catalytic reaction can be carried out in the presence of excess hypochlorite or periodate.[332,335]



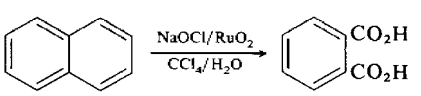
89% (118)

Carbon-carbon bonds can be selectively cleaved by ruthenium-oxo compounds, such as in the transformation of phenylcyclohexane to cyclohexanecarboxylic acid (equation 119).[332]



94% (119)

Polynuclear aromatic hydrocarbons are oxidatively cleaved by RuO_4 under mild conditions, and this reaction can be performed catalytically in the presence of NaOCl (equation 120).[336]



65% (120)

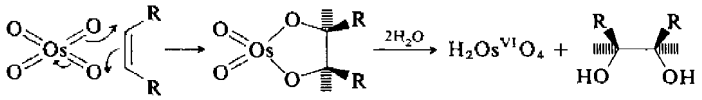
Dialkyl- and diaryl-acetylenes are selectively converted to α-diketones (equation 121), whereas terminal alkynes give the corresponding carboxylic acid with loss of one carbon atom.[337]

$$PhC{\equiv}CPh \xrightarrow[CCl_4\text{-}H_2O]{NaOCl/RuO_2} \underset{83\%}{PhC(=O)C(=O)Ph} \quad (121)$$

61.3.3.4.3 Oxidation by osmium–oxo compounds

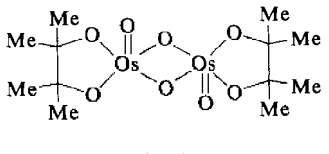
Osmium tetroxide is a mild, reliable reagent for the selective oxidation of alkenes to *cis*-1,2-glycols. Discovered a long time ago,[338,341] this reaction has been widely used for synthetic purposes by organic chemists.[290,342]

The Criegee mechanism originally proposed involves the formation of an osmium(VI)-ester complex (**106**) from the [4+2] cycloaddition of the Os^{VIII} *cis*-dioxo moiety with an alkene, followed by the hydrolysis or reduction of (**106**) to *cis*-glycol and reduced osmium species. In support of this mechanism a variety of Os^{VI} cyclic esters such as (**107**) or (**108**) (L = quinuclidine) have recently been synthesized from OsO_4 and the alkene, and characterized by an X-ray crystal structure.[290,343] In solution the dimeric complex (**108**) dissociates to give the monomeric dioxo trigonal-bipyramidal complex (**109**), which is similar to (**106**).[344]

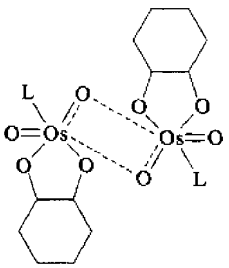


(122)

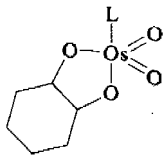
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(107)

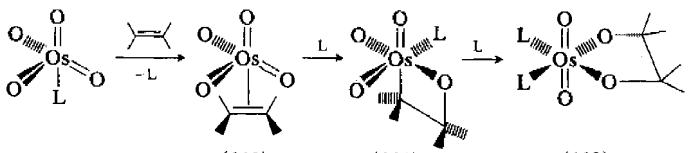


(108)



(109)

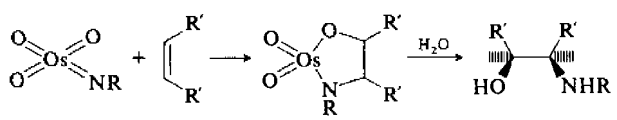
Sharpless and Hentges proposed that the cyclic ester (**112**) is formed *via* an oxametallacyclobutane (**111**) resulting from the [2+2] intramolecular addition of an oxo bond to the coordinated alkene in (**110**).[345] They utilized the high stereoselectivity of this reaction to induce chirality with good optical yields (up to 83%) during the hydroxylation of various alkenes by OsO_4 in the presence of chiral pyridine ligands.[345]



(123)

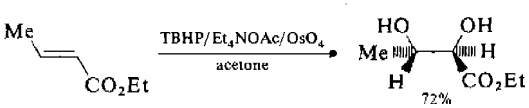
(110) (111) (112)

The same researchers found that imino derivatives of OsO_4 react with alkenes to produce *cis*-β-amino alcohols (equation 124).[346,347] This oxyamination reaction can be made catalytic in the presence of chloramine salts, *e.g.* $ArSO_2NClNa$ or $ROCONClAg$.[348,349]

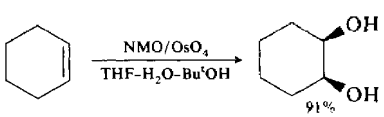


(124)

Since OsO_4 is volatile, toxic and expensive, considerable effort has been devoted to the catalytic application of the *cis* dihydroxylation of alkenes in the presence of excess cooxidant.[57,290] Previous procedures used metal chlorate (Hoffman reagent),[339] or hydrogen peroxide (Milas reagent)[350] as cooxidant, usually in Bu^{t}OH or acetone.[290] Recent procedures utilize *t*-butyl hydroperoxide in conjunction with ammonium salts (Et_4NOH or Et_4NOAc)[57,351] or *N*-methylmorpholine *N*-oxide,[352] and are generally more selective.



(125)



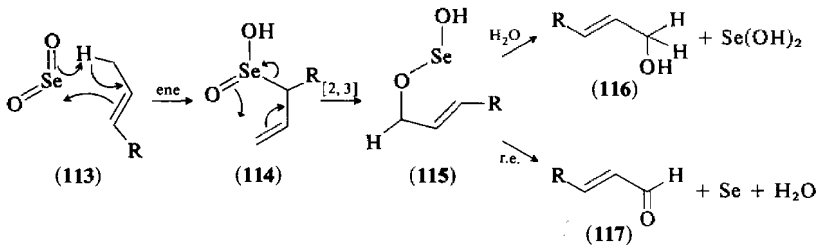
(126)

61.3.3.5 Selenium and Tellurium

61.3.3.5.1 Allylic oxidations by selenium dioxide

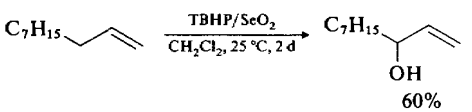
Selenium dioxide, SeO_2, is a widely used reagent for the allylic oxidation of alkenes and ketones. The subject has been extensively covered by recent review articles[56,291-293] and only a short summary will be given in this chapter.

The oxidation of alkenes by SeO_2 (or its hydrated form $SeO(OH)_2$) results in the formation of allyl alcohols and α,β-unsaturated compounds, or allylic acetate when the reaction is carried out in acetic acid. (a) The oxidation generally occurs without double bond rearrangement. (b) Oxidation of 2-methyl-2-alkenes occurs at the (*E*) methyl group. (c) 1-Substituted cyclohexene is oxidized at the 6-position; this rules out the formation of allylic free radicals or carbonium ions. The widely accepted mechanism of this reaction has been proposed by Sharpless:[353-355] it involves the initial ene addition (**113**) of the Se=O group to the alkene to form the allylseleninic acid (**114**), which undergoes a [2,3] sigmatropic rearrangement to give the allyl selenenate (**115**). The allyl alcohol (**116**) is formed by hydrolysis of (**115**), whereas the α,β-unsaturated carbonyl compound (**117**) results from the reductive elimination of (**115**), coproducing selenium metal in its colloidal form.

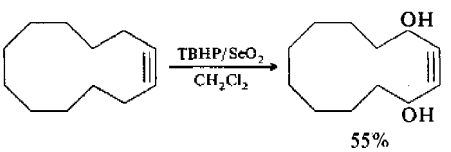


(113) (114) (115) (116) (117) (127)

Allyl alcohols can be produced catalytically by oxidation of alkenes with TBHP in the presence of small amounts of SeO_2 (equation 128). In contrast to the stoichiometric reaction, this catalytic oxidation can be performed under mild conditions (r.t., CH_2Cl_2 solvent).[356] Alkynic compounds undergo a predominant allylic dihydroxylation upon reaction with TBHP/CH_2Cl_2 (equation 129).[357]

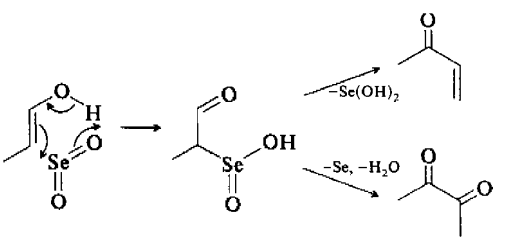


(128)



(129)

Selenium dioxide is a most useful reagent for the oxidation of ketones or aldehydes to α-dicarbonyl compounds along with α,β-unsaturated carbonyl compounds as by-products.[291,293] The carbonyl compound probably reacts in its enol form in a way similar to that of alkene oxidation (equation 130).[358]



(130)

61.3.3.5.2 Oxidation by tellurium–oxo compounds

The use of tellurium dioxide as an oxidation reagent has been seriously hampered by its very low solubility in almost all organic solvents. However, TeO_2 appears to be a much milder oxidant than SeO_2.

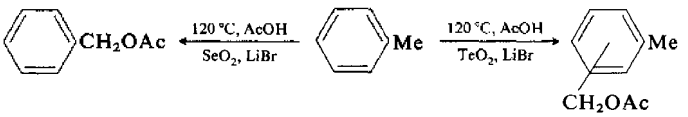
Catalytic systems containing TeO_2, HBr and AcOH have been used industrially by Oxirane to convert ethylene to ethylene glycol *via* the formation of mono- and di-acetate (equations 131 and 132).[359-361] The overall yield from ethylene to ethylene glycol is more than 90%, making this reaction competitive with respect to the older silver-catalyzed ethylene epoxidation process.

However, the development of this process has been suspended, largely because of corrosion problems.[361]

$$CH_2{=}CH_2 + 2AcOH + 0.5O_2 \xrightarrow[160\,^\circ C]{TeO_2/HBr} AcOCH_2CH_2OAc + H_2O \quad (131)$$

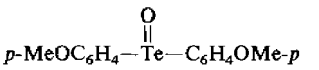
$$AcOCH_2CH_2OAc + 2H_2O \rightarrow HOCH_2CH_2OH + 2AcOH \quad (132)$$

A similar TeO_2/HBr catalyst has been used in acetic acid for the oxidation of propene at *ca.* 120 °C to propene oxide and propene glycol *via* 1,2-diacetoxypropane.[361,362] However, this reaction gives lower yields because of side allylic oxidation reactions. Oxidation of toluene under similar conditions (TeO_2/LiBr, 160 °C) results in the formation of methylbenzyl acetate mixtures rather than benzyl acetate as observed with SeO_2/LiBr catalyst (equation 133).[363]

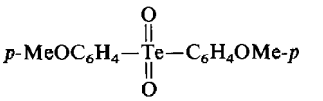


(133)

Bis(*p*-methoxyphenyl) telluroxide (**118**) and the corresponding tellurone (**119**) have recently been shown to exhibit mild oxidizing properties towards easily oxidizable substrates. Thus the telluroxide (**118**) oxidizes thiocarbonyl compounds RR'C=S to the corresponding ketone RR'C=O[364,365] and 3,4-di-*t*-butylpyrocatechol to 3,4-di-*t*-butyl-*o*-quinone.[364] The tellurone (**119**) oxidizes benzyl alcohols to the corresponding carbonyl compounds, a reaction which is not observed with (**118**).[366]



(**118**)



(**119**)

61.3.4 OXIDATION BY NUCLEOPHILIC ATTACK AT HYDROCARBON SUBSTRATES COORDINATED TO PALLADIUM

61.3.4.1 Introduction

Discovered by Phillips in 1894,[382] the oxidation of ethylene to acetaldehyde by palladium(II) salts in an aqueous solution was developed into a commercial process about 60 years later by Smidt and coworkers at Wacker Chemie.[383,384] These researchers succeeded in transforming this stoichiometric oxidation by a precious metal (equation 150) into a catalytic reaction through the reoxidation of the resulting Pd^0 by molecular oxygen in the presence of copper salts (equations 151–152).

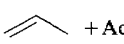
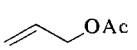
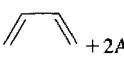
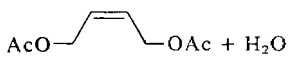
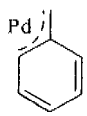
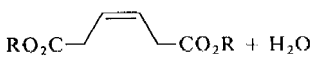
$$CH_2{=}CH_2 + PdCl_2 + H_2O \rightarrow MeCHO + Pd^0 + 2HCl \quad (150)$$

$$Pd^0 + 2CuCl_2 \rightarrow PdCl_2 + Cu_2Cl_2 \quad (151)$$

$$Cu_2Cl_2 + 2HCl + 0.5O_2 \rightarrow 2CuCl_2 + H_2O \quad (152)$$

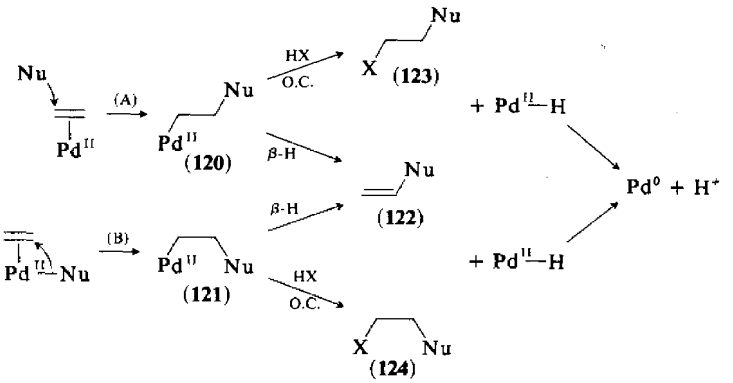
The commercial success of this reaction was a major step leading to the withdrawal of acetylene-based petrochemical technologies, and provided a considerable stimulus in both academic and industrial circles for research on homogeneous catalysis by noble-metal complexes. This is reflected in the appearance of several books and many review articles devoted to the organic chemistry of palladium.[367–370,384–394] Applications of palladium catalysts in organic synthesis, including oxidation reactions, have been extensively covered by Trost and Verhoeven in 'Comprehensive Organometallic Chemistry'.[395] This section will deal only with catalytic reactions in which molecular oxygen is involved as the palladium reoxidant. Table 6 lists some of these catalytic oxidations which involve ketonization, glycolate formation, acetoxylation, oxycarbonylation, oxycyanation, oxychlorination, oxidative coupling, oxidation of alcohols and oxidation by coordinated nitro ligands. Some of these reactions, *e.g.* the oxidation of ethylene to acetaldehyde and of propene to acetone, the acetoxylation of ethylene to vinyl acetate and of butadiene to 1,4-diacetoxy-2-butene, and the oxycarbonylation of methanol to dimethyl oxalate, have been the object of large-scale industrial development.

Table 6 Palladium-catalyzed Oxidation of Hydrocarbons

Catalytic reaction		*Complex*	*Nucleophile*	*Refs.*
Oxidation of alkenes to carbonyl compounds (Wacker)				
$RCH{=}CH_2 + 0.5O_2 \rightarrow RCOMe$	(134)		H_2O	56, 367-370
Oxidation of alkenes to glycolates				
$RCH{=}CH_2 + AcOH + 0.5O_2 \rightarrow RCH(OH)CH_2OAc$	(135)		AcOH	371
Acetoxylations				
$CH_2{=}CH_2 + AcOH + 0.5O_2 \rightarrow CH_2{=}CHCH_2OAc + H_2O$	(136)	Pd-II	AcOH	367-370
 $+ AcOH + 0.5O_2 \rightarrow$  $+ H_2O$	(137)		AcOH	367
 $+ 2AcOH + 0.5O_2 \rightarrow$  $+ H_2O$	(138)		AcOH	372
$PhMe + AcOH + 0.5O_2 \rightarrow PhCH_2OAc + H_2O$	(139)		AcOH	373
Oxycarbonylations				
$CH_2{=}CH_2 + CO + 0.5O_2 \rightarrow CH_2{=}CHCO_2H$	(140)	Pd-II	—	374
 $+ 2CO + 2ROH + 0.5O_2 \rightarrow$  $+ H_2O$	(141)		CO/ROH	375
$PhH + CO + 0.5O_2 \rightarrow PhCO_2H$	(142)	—	—	376
$RCH{=}CH_2 + CO + H_2O \rightarrow RCH(CO_2H)Me$	(143)	—	—	377
$2ROH + 2CO + 0.5O_2 \rightarrow RO_2C{-}CO_2R$	(144)	—	—	378
Oxycyanation				
$CH_2{=}CH_2 + HCN + 0.5O_2 \rightarrow CH_2{=}CHCN + H_2O$	(145)	Pd-II	HCN	379
Oxychlorination				
$CH_2{=}CH_2 + HCl + 0.5O_2 \rightarrow CH_2{=}CHCl + H_2O$	(146)	Pd-II	HCl	370
Oxidative coupling				
$2ArH + 0.5O_2 \rightarrow Ar{-}Ar + H_2O$	(147)	Pd—Ar	—	380
Oxidation of alcohols to carbonyl compounds				
$RR'CHOH + 0.5O_2 \rightarrow RR'C{=}O + H_2O$	(148)	—	—	381

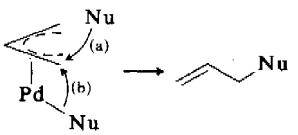
Most of the reactions listed in Table 6 involve prior activation of the substrate by coordination to palladium in the form of a π-, a π-allylic, a π-benzylic, or an alkyl or aryl complex. Once coordinated to the metal, the substrate becomes an electron acceptor and can react with a variety of different nucleophiles. The addition of nucleophiles (Nu) to the coordinated substrate may occur in two different ways, as shown by Scheme 9 for π-alkene complexes:[397-399] (a) external attack leading to *trans* addition of palladium and nucleophile across the π-system (path A); or (b) internal addition of the coordinated nucleophile to the complexed alkene resulting in *cis* addition of palladium and nucleophile to the double bond. The *cis* and *trans* adducts (**120**) and (**121**) may then undergo β-hydride elimination (β-H), producing the vinylic oxidation product

(**122**), or palladium–carbon oxidative cleavage (O.C.) to give the *cis* and *trans* addition products (**124**) and (**123**). During this reaction the palladium(II) complex is reduced to metallic palladium(0), probably *via* reductive elimination from the palladium hydride species.



Scheme 9

Nucleophilic attack at π-allylic complexes may also occur from (a) external *trans* addition or (b) internal *cis* addition, resulting in the formation of allylic oxidation products (equation 153).[398,399]



(153)

Bäckwall and coworkers have extensively studied the stereochemistry of nucleophilic additions on π-alkenic and π-allylic palladium(II) complexes. They concluded that nucleophiles which preferentially undergo a *trans* external attack are 'hard' bases such as amines, water, alcohols, acetate and stabilized carbanions such as β-diketonates. In contrast, 'soft' bases are nonstabilized carbanions such as methyl or phenyl groups and undergo a *cis* internal nucleophilic attack at the coordinated substrate.[398,399] The pseudocyclic alkylperoxypalladation procedure occurring in the ketonization of terminal alkenes by $[RCO_2PdOOBu^t]_4$ complexes (see Section 61.3.2.2.2)[42] belongs to internal *cis* addition processes, as well as the oxidation of complexed alkenes by coordinated nitro ligands (*vide infra*).[396,397]

61.3.4.2 Oxidation of Alkenes to Carbonyl Compounds

The stoichiometric oxidation of ethylene to acetaldehyde by $PdCl_2$ in an aqueous solution (equation 150) has the following characteristics.[367,368]

(i) At low Pd^{II} concentration the rate expression is:

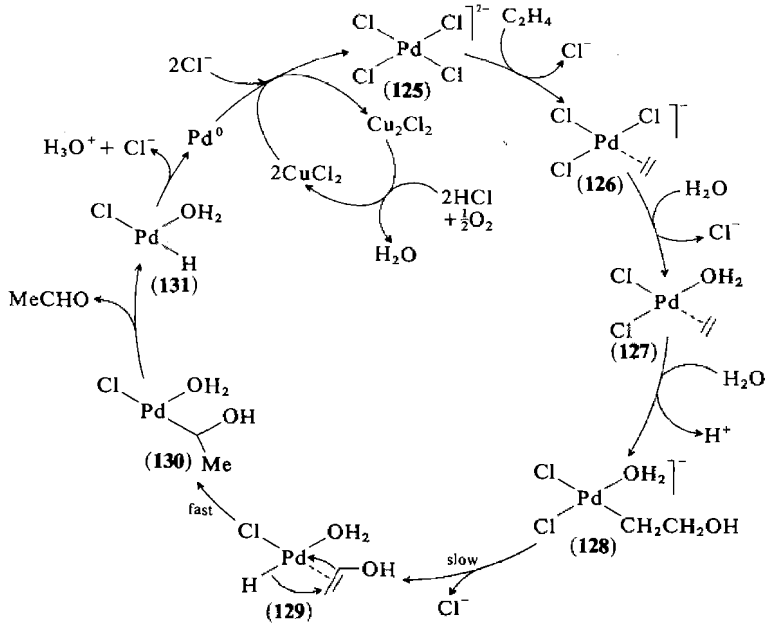
$$-d(C_2H_4)/dt = k[PdCl_4^{2-}][C_2H_4]/[Cl^-]^2[H^+].$$

(ii) No H/D exchange occurs when C_2H_4 is oxidized in D_2O, or when C_2D_4 is oxidized in H_2O.

(iii) The kinetic isotope effect k_H/k_D is 1.07 when C_2D_4 is oxidized in H_2O, and 4.05 when C_2H_4 is oxidized in D_2O.

The mechanism depicted in Scheme 10 satisfactorily accounts for most of the kinetic and stereochemical data concerning this reaction,[367,400,401] although some important details are still subject to debate.[367]

The key feature of this mechanism is the π–σ rearrangement of the coordinated alkene (**127**) → (**128**) and the ensuing β-hydride elimination (**128**) → (**129**). Although kinetic measurements favor an internal *cis* migration of the coordinated hydroxyl group to the alkene (or ethylene insertion into a Pd—OH bond),[367] recent stereochemical studies of oxidation[400] and oxycarbonylation[401] of *cis*- and *trans*-CHD=CHD indicate that the hydroxypalladation is *trans*, and probably results from the external nucleophilic attack of the coordinated ethylene by water. As for acetoxylation (*vide infra*), it is possible that both mechanisms operate, depending on the reaction conditions. The hydroxypalladation procedure has been convincingly illustrated by Moiseev who



Scheme 10

found that transmetalation of mercury by palladium in $HOCH_2CH_2HgCl$ results in the exclusive formation of acetaldehyde (equation 154).[402] This procedure has been used to obtain high yields of methyl ketones from higher terminal alkenes.[403]

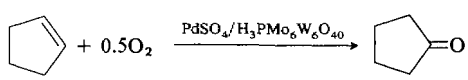
$$Cl{-}Hg{-}CH_2\underset{\underset{OH}{|}}{CHR} + PdCl_2 \xrightarrow[-HgCl_2]{} Cl{-}Pd{-}CH_2\underset{\underset{OH}{|}}{CHR} \rightarrow R{-}\underset{\underset{O}{\|}}{C}{-}Me + Pd^0 + HCl \qquad (154)$$

The commercial Wacker process for the manufacture of acetaldehyde operates in a single-stage or a two-stage procedure.[404] In the single-stage process, ethylene and oxygen are fed into a reactor containing an aqueous hydrochloric solution of $PdCl_2$ ($\sim 4\ g\ l^{-1}$) and a large excess of $CuCl_2$ ($\sim 200\ g\ l^{-1}$) at 120 °C and 4 atm pressure. Ethylene conversion is *ca.* 40%, and oxygen conversion is almost complete. Acetaldehyde is distilled out of the reaction mixture to remove the reaction heat ($\Delta H = -242\ kJ\ mol^{-1}$). In the two-stage process, ethylene reacts with the same catalyst solution at 105–110 °C and 10 atm until most of the Cu^{II} has been reduced to Cu^{I}. After distillation of the acetaldehyde, the aqueous catalyst solution is reoxidized by air in a second reactor, and then recycled to the first reactor. Both processes give 95% yields of acetaldehyde, together with acetic acid and chlorinated by-products.

A similar single- or two-stage process has been developed for the manufacture of acetone from propene (110–120 °C, 10 atm, $PdCl_2$–$CuCl_2$–HCl catalyst) but on a smaller scale (80 000 t/year) than for acetaldehyde (2 500 000 t/year).[405] The yield is *ca.* 93%.

Higher alkenes can also be converted to methyl ketones with the Wacker catalyst, but the rates and selectivities are lower. Improved procedures use basic[406,407] or alcoholic solvents.[408] Tsuji and coworkers used the $PdCl_2$/CuCl catalyst in DMF for the synthesis of a variety of natural products and fine chemicals.[409] Only terminal alkenes are ketonized under these conditions, even when the substrate contains other functional groups.[395]

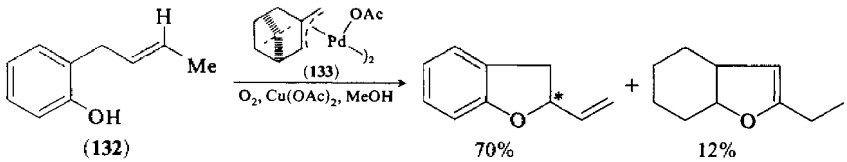
The Wacker $PdCl_2$–$CuCl_2$ catalyst is a highly corrosive one, and its use requires special vessels and apparatus, such as titanium or tantalum alloys. Heteropolyacids have been used as alternative noncorrosive reoxidants of palladium for a variety of organic transformations,[410] for example in reaction (155).[411]



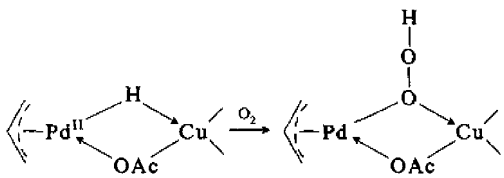
100% (155)

Good yields of carbonyl compounds have also been obtained from the vapor-phase oxidation of alkenes by steam and air over palladium catalysts supported on charcoal.[412] In this case, no copper cocatalyst is needed, presumably because palladium(II) is not reduced to palladium(0), but remains in the form of a stabilized palladium(II) hydride which can react with O_2 to give the hydroperoxidic species.

In fact, the role of copper and oxygen in the Wacker Process is certainly more complicated than indicated in equations (151) and (152) and in Scheme 10, and could be similar to that previously discussed for the rhodium/copper-catalyzed ketonization of terminal alkenes. Hosokawa and coworkers have recently studied the Wacker-type asymmetric intramolecular oxidative cyclization of *trans*-2-(2-butenyl)phenol (**132**) by O_2 in the presence of (+)-(3,2,10-η-pinene)palladium(II) acetate (**133**) and $Cu(OAc)_2$ (equation 156).[413] It has been shown that the chiral pinanyl ligand is retained by palladium throughout the reaction, and therefore it is suggested that the active catalyst consists of copper and palladium linked by an acetate bridge. The role of copper would be to act as an oxygen carrier capable of rapidly reoxidizing palladium hydride into a hydroperoxide species (equation 157).[413] Such a process is also likely to occur in the palladium-catalyzed acetoxylation of alkenes (see Section 61.3.4.3).

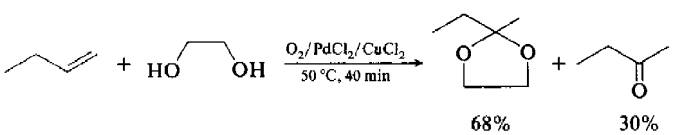


(156)

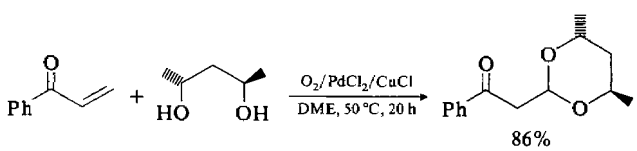


(157)

Acetalization of alkenes can be achieved in good yields when the oxidation is carried out in the presence of alcohols or diols. Acetalization of terminal alkenes such as 1-butene occurs preferentially at the 2-position in the presence of $PdCl_2$–$CuCl_2$ (equation 158),[414] whereas terminal alkenes bearing electron-withdrawing substituents are acetalized at the terminal position in the presence of $PdCl_2$–CuCl in 1,2-dimethoxyethane (equation 159).[415]



(158)



(159)

61.3.4.3 Acetoxylation of Alkenes, Dienes and Aromatic Hydrocarbons

61.3.4.3.1 Vinyl acetate from ethylene

First discovered by Moiseev *et al.*,[416] the palladium-catalyzed acetoxylation of ethylene to vinyl acetate has been the subject of very active investigations, particularly in industry, as shown by the considerable number of patents existing in this area. Vinyl acetate is an extremely important petrochemical product which is used for the synthesis of polymers such as poly(vinyl acetate) and poly(vinyl alcohol). Most of its annual production (~2.6 Mt) results from the acetoxylation of ethylene (equation 160).

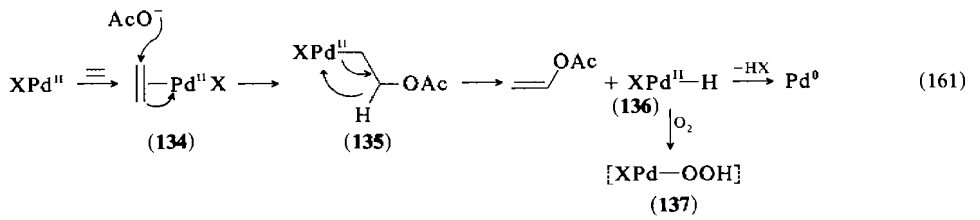
$$CH_2{=}CH_2 + AcOH + 0.5O_2 \xrightarrow{Pd} CH_2{=}CHOAc + H_2O \qquad (160)$$

The vinyl acetate process exists in both homogeneous and heterogeneous versions. The liquid-phase process developed by ICI is essentially a Wacker reaction performed in acetic acid: ethylene, O_2 and AcOH are reacted at 110 °C in the presence of $PdCl_2$, $Cu(OAc)_2$ and HCl. Overall yields are greater than 90%. Acetaldehyde is formed as a coproduct in the reaction, owing to the presence

of water, and is oxidized to acetic acid which is used in the process. However, this process encountered severe corrosion problems and was abandoned.[94]

The gas-phase process, successfully commercialized independently by Bayer and USI,[417] involves passing a mixture of ethylene, acetic acid and oxygen over a supported palladium catalyst contained in a multitubular reactor at 150 °C and about 5–10 atm pressure. The overall yield in vinyl acetate is about 92%, and the major by-product is CO_2. The catalyst consists of a palladium salt (*e.g.* Na_2PdCl_4) deposited on silica (or alumina) in the presence of a cocatalyst (*e.g.* $HAuCl_4$), reduced and impregnated with potassium acetate before use.[384,418] The lifetime of the catalyst is about 2 years.[417]

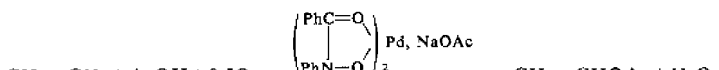
A widely accepted mechanism for acetoxylation of ethylene is shown in equation (161) and consists of the nucleophilic attack of the acetate anion on the coordinated ethylene, followed by acetoxypalladation and β-hydride elimination, giving vinyl acetate and palladium hydride.[367]



(161)

It should be noted that heterogeneous palladium acetoxylation catalysts do not contain copper cooxidants, presumably because the support stabilizes the resulting palladium(II) hydride such as (**136**) and prevents the formation of metallic palladium. The stabilized palladium hydride (**136**) may react with O_2 to give the hydroperoxide (**137**), which is probably an important intermediate for the regeneration of the initial Pd^{II} catalyst.

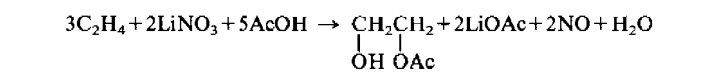
Such a stabilization of the palladium catalyst can also be achieved in homogeneous liquid phase by the use of appropriate ligands. Thus, it has recently been shown that palladium(II) hydroxamates are effective catalysts for the acetoxylation of ethylene with high selectivity and a high turnover (>200) (equation (162), whereas $Pd(OAc)_2$ rapidly becomes deactivated and precipitates in the form of metallic palladium.[419] It is probable that the bidentate hydroxamate ligand stabilizes the hydride Pd—H species and prevents palladium from precipitating.



(162)

61.3.4.3.2 Oxidation of ethylene to glycol acetate

When palladium-catalyzed acetoxylation is carried out in the presence of nitrate or nitrite ions, ethylene glycol monoacetate (EGMA) results as the major product of the reaction (equation 163).[420]



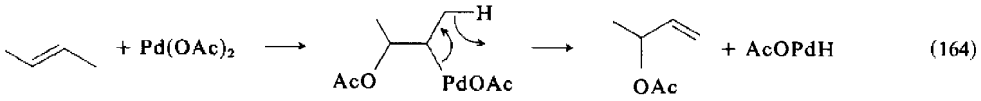
(163)

This reaction can be made catalytic by reoxidizing the resulting nitric oxide to nitric acid by air, and has been developed into a commercial process by Kuraray for the manufacture of ethylene glycol from the hydrolysis of EGMA.[421] The overall yield of ethylene glycol in this process is *ca.* 95%. The mechanism of EGMA formation (equation 163) has not been studied intensively, but it is generally thought that EGMA results from the oxidative cleavage of the acetoxypalladation adduct (**135**; equation 161) by nitrite or nitrate ions which prevent β-hydride elimination.[361] Yermakov *et al.* have recently shown, by ^{17}O NMR studies, that the oxygen carbonyl atom of EGMA is derived from $LiNO_3$, and have therefore suggested that palladium(II)-nitro species are involved as the actual oxidizing species.[422]

61.3.4.3.3 Allylic acetoxylation of alkenes

In contrast to ethylene, which gives only vinylic or oxidative addition products, the acetoxylation of higher alkenes results in the formation of a mixture of allylic and vinylic acetates.[367] The

selectivity of this reaction can be controlled by adjusting the oxidation conditions. Thus the oxidation of propylene by $PdCl_2$ in acetic acid without added acetate gives 96% 2-propenyl acetate, whereas allylic acetate is the major product (94%) when the same reaction is carried out in the presence of excess sodium acetate.[422a] Although π-allylic complexes are remarkably stable, the allylic oxidation of alkenes seems to proceed *via* a classical acetoxypalladation–palladium hydride elimination rather than from π-allyl routes.[423] β-Hydride elimination preferentially occurs at the carbon center not containing the acetate group (equation 164).



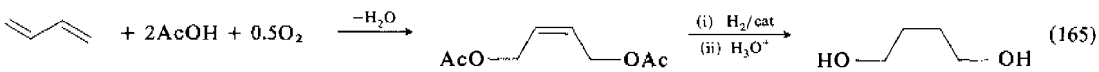
(164)

Both homogeneous and heterogeneous procedures have been developed for the synthesis of allyl acetate from propene (equation 137 and Table 6). Allyl acetate is an interesting intermediate which can be hydrolyzed to allyl alcohol,[424] or hydroformylated to a 1,4-butanediol or THF precursor.[425]

Acetoxylation of propene to allyl acetate can be performed in the liquid phase with high selectivity (98%) in acetic acid in the presence of catalytic amounts of palladium trifluoroacetate.[426] The stability and activity of this catalyst can be considerably increased by adding copper (II) trifluoroacetate and sodium acetate as cocatalysts (100 °C, 15 bar, reaction time = 4 h, conversion = 70%, selectivity = 97%). Gas-phase procedures for the manufacture of allyl acetate are described in several patents and use conventional palladium catalysts deposited on alumina or silica, together with cocatalysts (Au, Fe, Bi, *etc.*) and sodium acetate. The activity and selectivity reported for these catalysts are very high (100–1000 g l^{-1} h^{-1}, selectivity = 90–95%).[427] A similar procedure has been used for the synthesis of methallyl acetate from 2-methylpropene.[428]

61.3.4.3.4 Acetoxylation of dienes

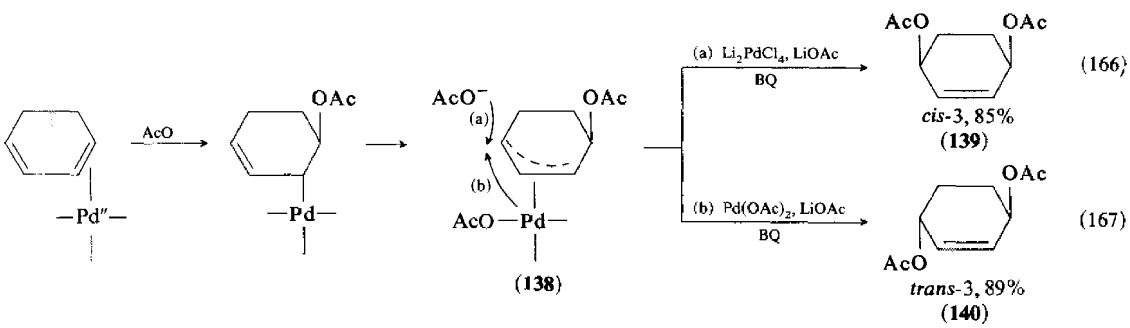
Palladium-catalyzed 1,4-diacetoxylation of butadiene is a useful reaction of commercial interest which provides an interesting alternative for the synthesis of butanediol and tetrahydrofuran, previously based on acetylene feedstocks (equation 165).



(165)

The selectivity in the formation of 1,4-diacetoxy-2-butene (1,4-DAB) is considerably enhanced when tellurium compounds are used as cocatalysts. Thus a heterogeneous catalyst, prepared by impregnation of $Pd(NO_3)_2$ and TeO_2 dissolved in HNO_3 over active charcoal (Pd/Te = 10), can be used for the oxidation of butadiene (by O_2 in AcOH at 90 °C) to 63% *trans*-1,4-DAB, 25% *cis*-1,4-DAB and 12% 3,4-diacetoxy-1-butene. Conventional soluble catalysts such as $Pd(OAc)_2$/Li(OAc) are much less selective in the formation of 1,4-DAB.[429] The gas-phase 1,4-diacetoxylation of butadiene in the presence of Pd-Te catalysts is currently being industrially developed by Mitsubishi and BASF.[430]

The mechanism of 1,4-diacetoxylation of dienes and its stereochemical aspects have been studied in great detail by Bäckwall and coworkers.[397–399] Thus the 1,4-diacetoxylation of 1,3-cyclohexadiene mainly occurs *trans* in the presence of $Pd(OAc)_2$/LiOAc/benzoquinone (BQ) (equation 167), whereas the use of an Li_2PdCl_4/LiOAc/BQ system results in the major formation



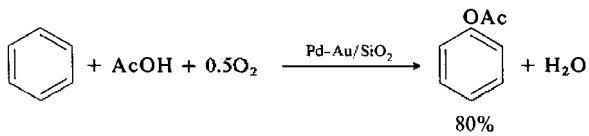
(166)

(167)

of *cis*-1,4-diacetoxy-2-cyclohexene (equation 166). The mechanism involves 1,2-acetoxypalladation of the diene followed by nucleophilic attack of the resulting π-allylic complex (**138**) by the coordinated acetate, giving the *trans* product (**140**; path b). In the presence of chloride ligands, external acetate addition on (**138**) occurs and gives rise mainly to formation of the *cis* isomer (**139**).[399]

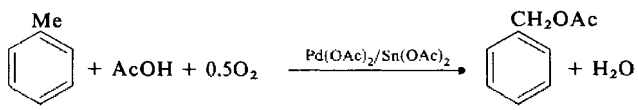
61.3.4.3.5 Acetoxylation of aromatic compounds

The reaction of palladium(II) salts with benzene in acetic acid gives a mixture of biphenyl and phenyl acetate.[431] Nuclear acetoxylation is favored by the presence of sodium acetate, whereas oxidative arene coupling occurs at high oxygen pressure. The acetoxylation of benzene to phenyl acetate can be made catalytic in the presence of strong oxidants such as $K_2Cr_2O_7$.[432] Supported palladium catalysts appear to have greater stability for the gas-phase acetoxylation of benzene. High yields of phenyl acetate can be obtained from the reaction of benzene, acetic acid and oxygen over Pd-Au/SiO_2 catalysts at 150 °C (equation 168).[433] This reaction is of industrial interest as a more direct route to phenol than the conventional cumene oxidation process.

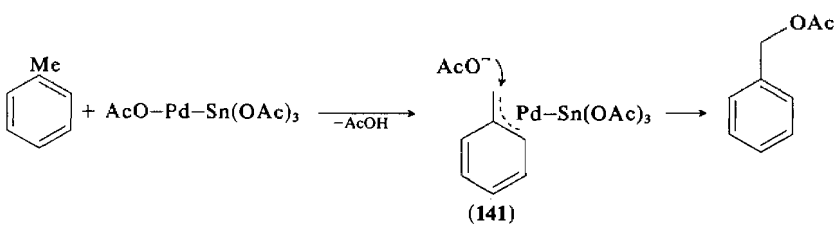


(168)

Acetoxylation of toluene using a $Pd(OAc)_2$-$Sn(OAc)_2$-charcoal catalyst selectively produces benzyl acetate with high turnover numbers (~100).[373,434] The active catalyst presumably contains Pd—Sn bonds. Tin ligands are known to increase the π-acceptor ability of palladium, and may favor the coordination of the toluene in the form of a benzylic π-allyl complex (**141**) which is nucleophilically attacked by the acetate anion.[435]



(169)

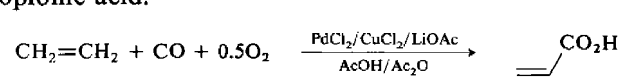


(170)

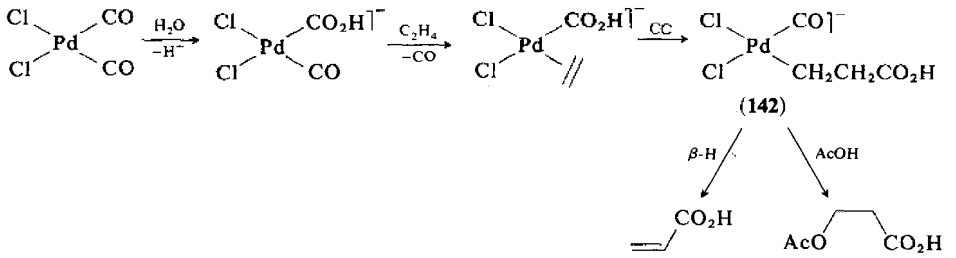
61.3.4.4 Oxycarbonylations

61.3.4.4.1 Alkenes and dienes

The reaction of carbon monoxide with alkenes in the presence of palladium catalysts under oxidative conditions has been extensively studied owing to its industrial importance (equation 171).[361,436–438] The oxidative carbonylation of ethylene to acrylic acid has been developed into a commercial process by Union Oil.[439] The reaction is performed at 150 °C, 77 atm, $C_2H_4/CO = 1$, in an acetic acid-acetic anhydride solvent mixture, and in the presence of a Wacker catalyst ($PdCl_2/CuCl_2/LiOAc$). Acrylic acid is produced as the main product, together with β-acetoxypropionic acid (overall yield = 80%). The suggested mechanism (equation 172) involves intramolecular insertion of coordinated ethylene into a palladium-carboxylic group obtained by water hydrolysis of the Pd-CO species. Acrylic acid results from β-hydride elimination of the carboxypalladation intermediate (**142**), whereas oxidative cleavage by AcOH results in the formation of β-acetoxypropionic acid.[440]



(171)



(172)

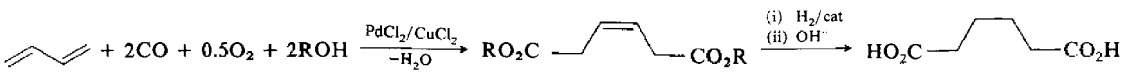
The oxycarbonylation of propene under the same conditions results in the formation of crotonic acid as the major product instead of the more valuable methacrylic acid.[439] When the oxycarbonylation of ethylene or terminal alkenes is carried out in anhydrous alcoholic solvents instead of acetic acid, dialkyl succinates and β-alkoxy esters are the major products (equation 173).[441,442]

$$R'CH{=}CH_2 \xrightarrow[PdCl_2/CuCl_2]{O_2/CO/ROH} R'CH(CO_2R)CH_2CO_2R + R'CH(OR)CH_2CO_2R \quad (173)$$

Non-oxidative hydrocarboxylation of alkenes to carboxylic acids with CO and H_2O is catalyzed by palladium complexes such as $PdCl_2(PhCN)_2$ or $PdCl_2(PPh_3)_2$, and α-methyl acids predominate in the presence of HCl.[374,443] A recent improvement of this reaction consisted of the use of a $PdCl_2/CuCl_2/HCl$ catalyst under oxidative conditions.[377] Almost quantitative yields of α-methyl carboxylic acids and dicarboxylic acids were obtained from terminal alkenes and terminal dialkenes respectively, at room temperature and atmospheric pressure (equation 174).[377]

$$RCH{=}CH_2 + CO + H_2O \xrightarrow[O_2,\ r.t.,\ 1\ atm]{PdCl_2/CuCl_2/HCl} RCH(Me)CO_2H \quad (174)$$

The synthesis of dialkyl hex-3-ene-1,6-dioate from the dioxycarboxylation of butadiene in an alcoholic solvent, and in the presence of a dehydrating agent such as trimethyl orthoformate[444] or 1,1-dimethoxycyclohexane,[445] provides an economically attractive route for the synthesis of adipic acid (equation 175).



(175)

61.3.4.4.2 Aromatic compounds

The oxidative carbonylation of arenes to aromatic acids is a useful reaction which can be performed in the presence of Wacker-type palladium catalysts (equation 176). The stoichiometric reaction of $Pd(OAc)_2$ with various aromatic compounds such as benzene, toluene or anisole at 100 °C in the presence of CO gives aromatic acids in low to fair yields.[446] This reaction is thought to proceed *via* CO insertion between a palladium–carbon (arene) σ-bond. It can be made catalytic in the presence of excess TBHP and allyl chloride, but substantial amounts of phenol and coupling by-products are formed.[447]

$$ArH + CO + 0.5O_2 \xrightarrow{Pd/Cu} ArCO_2H \quad (176)$$

The catalytic oxycarbonylation of benzene and naphthalene to benzoic or naphthoic acid in the presence of Wacker-type catalysts has been reported in several patents,[376,448] but difficulties in reoxidizing the reduced palladium have inhibited industrial use of this chemistry.

61.3.4.4.3 Alcohols and phenols

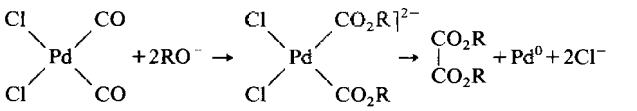
The synthesis of dialkyl oxalates by oxycarbonylation of alcohols in the presence of a dehydrating agent and a Wacker catalyst was first reported by Fenton in 1968 (equation 177).[378,449] As for the previous oxycarbonylations, the presence of water is a strong inhibitor of the reaction and favors the side-formation of CO_2 (equation 178). Dehydrating agents such as triethyl orthoformate or boric anhydride are necessary to prevent water formation and subsequent deactivation of the

catalyst. Improved procedures use $Pd(OAc)_2/Co(OAc)_2/PPh_3$/benzoquinone as a catalyst system and enable the oxycarbonylation of methanol by CO and dioxygen (yield = 83%, turnover number = 140).[450]

$$2ROH + 2CO + 0.5O_2 \xrightarrow[HC(OEt)_3]{PdCl_2/CuCl_2} RO_2CCO_2R + H_2O \quad (177)$$

$$PdCl_2 + CO + H_2O \rightarrow Pd + CO_2 + 2HCl \quad (178)$$

A likely mechanism for this reaction involves the nucleophilic attack of alcohol on two molecules of coordinated CO, followed by the coupling of the two palladium-bonded alkoxycarbonyl moieties (equation 179).[438,451] In support of this mechanism, the reaction of the bis(methoxycarbonyl) complex (**143**) with CO and PPh_3 produces dimethyl oxalate and the reduced palladium(0) complex.[451]



(179)

$$(PPh_3)_2Pd(CO_2Me)_2 \xrightarrow{CO,\ PPh_3} Pd(CO)(PPh_3)_3 + (CO_2Me)_2 \quad (180)$$

(**143**)

The synthesis of dimethyl oxalate and ethylene glycol from methanol, CO and H_2 is currently being industrially developed by UBE and Union Carbide.[452] Methyl nitrite is readily obtained from the reaction of methanol with nitric oxide in the presence of oxygen (equation 181). The carbonylation of methyl nitrite to dimethyl oxalate is achieved over a palladium/charcoal heterogeneous catalyst at 110–140 °C and low pressure (equation 182), and the resulting nitric oxide is recycled to the formation of methyl nitrite. Hydrogenolysis of dimethyl oxalate over a copper chromite catalyst results in the formation of ethylene glycol (equation 183). The overall yield of ethylene glycol in the combined steps is 90%. This syn-gas route to ethylene glycol might compete in the near future with older ethylene-based oxidation processes.

$$2MeOH + 2NO + 0.5O_2 \xrightarrow[3\ atm]{50\,^\circ C} 2MeONO + H_2O \quad (181)$$

$$2MeONO + 2CO \xrightarrow[110\text{–}140\,^\circ C,\ 3\ atm]{Pd/C} \underset{CO_2Me}{\overset{CO_2Me}{|}} + 2NO \quad (182)$$

90%

$$\underset{CO_2Me}{\overset{CO_2Me}{|}} + 4H_2 \xrightarrow[240\,^\circ C,\ 150\ atm]{Cu\ cat} \underset{CH_2OH}{\overset{CH_2OH}{|}} + 2MeOH \quad (183)$$

90%

The oxycarbonylation of phenol in the presence of a palladium catalyst, a tertiary amine and a manganese cocatalyst at room temperature and atmospheric pressure results in the formation of diphenyl carbonate in good yield (equation 184).[453]

$$2PhOH + CO + O_2 \xrightarrow[NEt_3]{PdBr_2/Mn(acac)_3} PhO{-}\overset{\overset{O}{\|}}{C}{-}OPh + H_2O \quad (184)$$

61.3.4.5 Miscellaneous Oxidations

61.3.4.5.1 Oxycyanation and oxychlorination

Ethylene stoichiometrically reacts with $Pd(CN)_2$ in benzonitrile at 150 °C to give acrylonitrile in 55% yield. This reaction can be performed catalytically by reacting ethylene, hydrogen cyanide and oxygen at 350 °C over $PdCl_2/V_2O_5/CsCl$ supported on alumina. The selectivity in acrylonitrile is about 90%, and the productivity about 20 g/g Pd/hour (equation 185).[379]

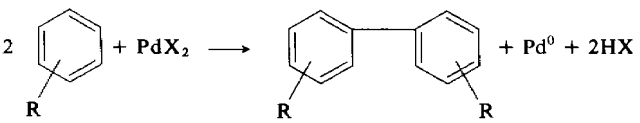
$$CH_2{=}CH_2 + HCN + 0.5O_2 \xrightarrow{Pd/V/Cs/Al_2O_3} CH_2{=}CHCN + H_2O \quad (185)$$

The catalytic oxychlorination of ethylene with HCl and O_2 to vinyl chloride can be catalyzed in the liquid phase by a $PdCl_2$–$CuCl_2$ mixture, or in the vapor phase over supported palladium

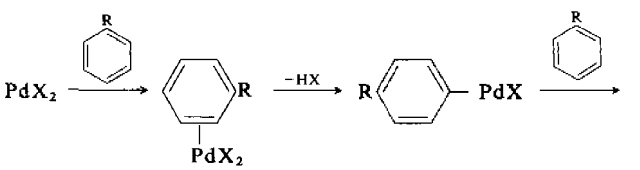
catalysts (equation 146).[370,454] However, these processes are not productive enough to compete with the conventional dehydrochlorination of 1,2-dichloroethane.

61.3.4.5.2 Oxidative coupling of arenes and alkenes

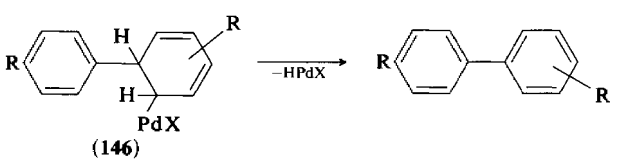
This reaction has been thoroughly reviewed,[367,455–458] and will be considered only briefly here. A variety of aromatic compounds can be oxidatively coupled by reaction with palladium(II) salts, *e.g.* $PdCl_2$, $Pd(OAc)_2$, $Pd(TFA)_2$ or $Pd(ClO_4)_2$, at a temperature generally not exceeding 120 °C (equation 186). In the general case, a mixture of all the theoretically possible biaryl isomers is formed, with their proportions depending on the nature of the substituent R. The reactivity of arenes increases with increasing nucleophilic substitution of the aromatic ring. The reaction is thought to proceed *via* π-arene (**144**), σ-arylpalladium (**145**) and arylpalladation of a second arene molecule to give (**146**), followed by β-hydride elimination.[455]



(186)

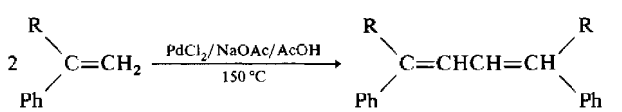


(187)



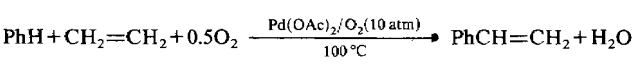
A catalytic arene-arene coupling can occur in the presence of cooxidants such as Cu^{II}, Fe^{III} and heteropolyacids along with molecular oxygen, but this reaction is still not selective enough for industrial use.

Oxidative coupling of specific alkenes such as styrene derivatives[459] and vinyl acetate[460] to 1,3-diene derivatives can also be achieved in the presence of palladium catalysts.[367,455] This coupling essentially occurs 'head to head', *i.e.* the C—C bond formation involves the least substituted carbon atoms of the double bonds (equation 188).[461]



(188)

The alkene arylation reaction has been extensively studied by Moritani and coworkers[462] and by Heck.[463] An interesting application of this chemistry is the synthesis of styrene from the oxidative coupling of benzene and ethylene (equation 189).[464]



(189)

650%/Pd

61.3.4.5.3 Oxidation of alcohols to carbonyl compounds

Palladium compounds are effective catalysts for the selective oxidative transformation of primary and secondary alcohols into carbonyl compounds. Although conventional $PdCl_2/CuCl_2$ catalysts can operate at 70–120 °C and under O_2 pressure (3 atm),[465] milder procedures using a $PdCl_2$/NaOAc mixture are effective at room temperature and atmospheric O_2 pressure (equation

190).[466] The mechanism of this transformation presumably involves palladium alkoxide formation followed by β-hydride elimination (equation 191).

$$R^1R^2CHOH + 0.5O_2 \xrightarrow[38\,^\circ C]{PdCl_2/NaOAc} R^1R^2C{=}O + H_2O \quad (190)$$

$$R^1R^2CHOH + PdX_2 \xrightarrow[-HX]{} XPd{-}O{-}\underset{H}{\overset{R^1}{\underset{|}{C}}}{-}R^2 \rightarrow R^1R^2C{=}O + HPdX \quad (191)$$

61.3.5 OXIDATION BY COORDINATED NITRO LIGANDS

It has been shown in the previous sections that only a very few catalytic systems are able to transfer both oxygen atoms of the dioxygen molecule onto two molecules of substrate. Representative examples are, in peroxide chemistry, the rhodium-catalyzed ketonization of alkenes by O_2, and, in oxo chemistry, the oxidation of phosphines to phosphine oxides in the presence of molybdenum dithiocarbamate. A recent interesting approach uses the oxidizing properties of coordinated nitro groups towards organic substrates S (equation 192) and the ensuing reoxidation of the reduced nitrosyl group by molecular oxygen to the initial nitro species (equation 193) to form a catalytic system.[467]

$$MNO_2 + S \rightarrow MNO + SO \quad (192)$$

$$MNO + 0.5O_2 \rightarrow MNO_2 \quad (193)$$

61.3.5.1 Oxidation by Cobalt–Nitro Complexes

Five-coordinate cobalt(III)-nitrosyl complexes possessing bent geometries react, in the presence of bases (*e.g.* L = pyridine), with molecular oxygen to give cobalt(III)-nitro complexes.[468,469] This reaction is generally thought to proceed *via* the formation of the bimetallic peroxy-nitrate intermediate (**147**).[470] The related pyCo(saloph)NO_2 complex [saloph = N,N′-bis(salicylidene)-*o*-phenylenediaminato] has been used as a stoichiometric oxidant of PPh_3 to PPh_3O and $MoO(S_2CNR_2)_2$ to $MoO_2(S_2CNR_2)_2$. The oxidation of phosphines to phosphine oxides becomes catalytic in the presence of dioxygen (equation 195).[471]

$$2(salen)Co{-}NO + O_2 \xrightarrow{L} L(salen)Co{-}N\underset{O-O}{\overset{O\quad O}{\diagup\diagdown}}N{-}Co(salen)L \rightarrow 2L(salen)Co{-}NO_2 \quad (194)$$

(**147**)

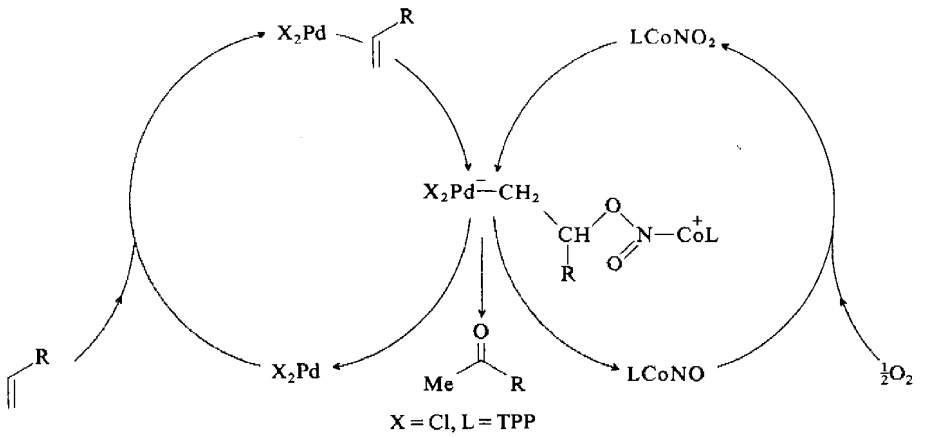
$$Co(saloph)(Py)(NO_2) \xrightarrow{Ph_3P \;\rightarrow\; Ph_3PO} Co(saloph)NO \quad (195)$$

$$Co(saloph)NO \xrightarrow{0.5O_2,\ py} Co(saloph)(Py)(NO_2)$$

Schiff base-cobalt-nitro complexes are too mild as oxidants to react as such with alkenes. However, the addition of Lewis acids (*e.g.* $BF_3 \cdot Et_2O$, $LiPF_6$) to these complexes activates the nitro ligand and produces a variety of both stoichiometric and catalytic oxidations. Stoichiometric transformations involve the oxidation of sulfides to sulfoxides and 1,3-cyclohexadiene to benzene.[467] Alcohols such as benzyl alcohol and cycloheptanol are catalytically transformed into the corresponding carbonyl compounds.[467,474]

$$2R^1R^2CHOH + 0.5O_2 \xrightarrow[60\,^\circ C]{pyCo(TPP)NO_2/BF_3} \underset{400\text{–}800\%/Co}{2R^1R^2C{=}O + H_2O} \quad (196)$$

Oxygen-transfer reactions have been shown to occur from cobalt(III)-nitro complexes to alkenes coordinated to palladium.[472] Thus ethylene and propene have been oxidized stoichiometrically in quantitative yields to acetaldehyde and acetone respectively, with the concomitant reduction of the nitro- to the nitrosyl-cobalt analog. A catalytic transformation with turnover numbers of 4–12 can be achieved at 70 °C in diglyme. The mechanism shown in Scheme 11 has been suggested.



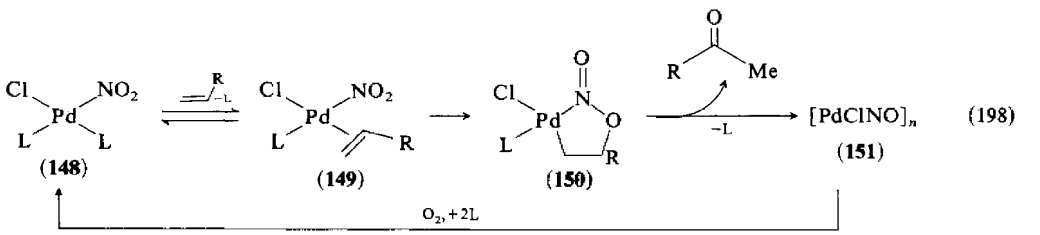
Scheme 11

A somewhat similar catalytic acetoxylation of ethylene to vinyl acetate by O_2 has been carried out in acetic acid in the presence of a $Pd(OAc)_2$-pyCo(TPP)NO_2 system.[472] A stoichiometric epoxidation of alkenes such as 1-octene or propene by cobalt-nitro complexes has been shown to occur in the presence of thallium(III) benzoate. Oxygen labeling studies showed that the epoxide oxygen atom comes only from the nitro ligand (equation 197).[473]

$$\text{pyCo(TPP)NO}_2 + \text{RCH=CH}_2 \xrightarrow{\text{Tl}^{III}} \text{Co(TPP)NO} + \text{RCH(O)CH} + \text{py} \qquad (197)$$

61.3.5.2 Oxidation of Alkenes by Palladium(II)- and Rhodium(III)-Nitro Complexes

Andrews and coworkers have recently shown that bis(acetonitrile)(chloro)(nitro)palladium(II) (**148**) stoichiometrically reacts with terminal alkenes to give the corresponding methyl ketone in almost quantitative yields and a reduced $[PdCl(NO)]_n$ complex. When the same reaction is carried out in the presence of dioxygen, a slightly catalytic production of 2-alkanone occurs (2-7 turnovers).[396] Labeling experiments with ^{18}O-enriched complex (**148**) clearly showed that the ketonic oxygen comes from the coordinated nitro group. More interestingly, a palladium-π-alkene complex (**149**) and a relatively stable five-membered metallacyclic intermediate (**150**) were detected during the reaction of (**148**) with propene.[396] All these data are consistent with the following mechanism (equation 198; L = MeCN).

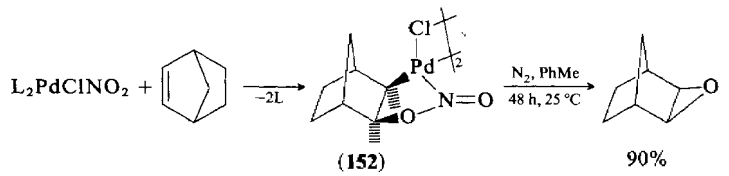


(198)

It is noteworthy that the metallacycle (**150**) strongly resembles the pseudocyclic intermediate (**84a**) postulated in the mechanism of ketonization of terminal alkenes by palladium(II)-*t*-butyl peroxide complexes (Scheme 6). On the basis of decomposition studies of platinametallacycles,[475] Andrews favored the cleavage of (**150**) between the Pd—N bond, in order to obtain a 0° Pd—C—C—H dihedral angle which is necessary for the ensuing β-hydride elimination to occur.[210] However, owing to the high strength of the Pd—N bond, which is illustrated by the formation of the resulting Pd—NO complex (**151**), plausible alternative mechanisms involving breakdown of the metallacycle (**150**) by a [C-β, C-α] hydride shift as in equation (58), or a [C-β, O-β] hydride shift as in equation (59), should also be considered.

The reaction of (**148**) with norbornene produces a stable, well-characterized bright yellow metallacyclic compound (**152**) which, upon standing at 25 °C in toluene, slowly decomposes to give *exo*-epoxynorbornene in almost quantitative yield (equation 199).[210] The particular decomposition, which is related in some aspects to the mechanism of alkene epoxidation by d^0 metal-peroxo

and -alkylperoxo species, can occur because norbornene has no possibilities for β-hydride elimination, π-allyl complex formation or hydride shift. Norbornene and some of its derivatives can be catalytically epoxidized by O_2 in the presence of (**148**) with 4–6 turnover numbers.[476]



(**152**) 90% (199)

The cationic rhodium(III)–nitro complex $[(MeCN)_4RhNO_2]^{2+}(BF_4)_2$ also oxidizes ethylene and 1-octene to acetaldehyde and 2-octanone, respectively. However, no catalytic oxidation takes place in the presence of dioxygen.[477]

61.3.6 CATALYSIS BY FIRST-ROW TRANSITION METAL COMPLEXES (Mn, Fe, Co, Cu)

61.3.6.1 Introduction

The oxidation chemistry of first-row transition metals has attracted considerable interest in recent decades owing to its close relationship with important biological processes. However, the mechanism of these oxidative processes still remains poorly understood, mainly because the characterization of reactive intermediates is difficult. Thus, neither peroxide examples of manganese, iron and copper nor their oxo derivatives of medium oxidation state have as yet been isolated and characterized by X-ray crystallography. Oxidation catalysis by Mn, Fe, Co and Cu is mainly homolytic in nature. These metals, which are characterized by one-electron oxidation-reduction steps, act in their oxidized form as one-electron oxidants and generally produce radical species from hydrocarbons. The direct interaction of cobalt(III) acetate or manganese(III) acetate with hydrocarbons is generally thought to proceed in two ways: (a) electron-transfer reaction (equations 200 and 201) and (b) electrophilic substitution at the metal center (equations 202 and 203).[56] Both processes involve one-electron reduction of the metal and concomitant carbon radical formation from the hydrocarbon and depend on both the oxidation-reduction potential of the metal [$E°$ (aqueous solution) = 1.82 V for Co^{3+}/Co^{2+} and 1.51 V for Mn^{3+}/Mn^{2+}] and the ionization potential of the hydrocarbon.[56]

Electron transfer

$$M(OAc)_3 + RH \rightleftarrows M(OAc)_3^- + RH^+ \quad (200)$$

$$RH^+ \rightarrow R\cdot + H^+ \quad (201)$$

Electrophilic substitution

$$M(OAc)_3 + RH \rightarrow RM(OAc)_2 + AcOH \quad (202)$$

$$RM(OAc)_2 \rightarrow R\cdot + M(OAc)_2 \quad (203)$$

In the presence of dioxygen, the carbon radical R· produced by reactions (201) and (202) ar transformed into alkylperoxy radicals ROO·, reacts with Co^{II} or Mn^{II} species to regenerate th Co^{III} or Mn^{III} oxidants, and produce primary oxygenated products (alcohol, carbonyl compounds, which can be further oxidized to carboxylic acids. This constitutes the basis of several industri processes such as the manganese-catalyzed oxidation of *n*-alkenes to fatty acids, and the cobal catalyzed oxidation of butane (or naphtha) to acetic acid, cyclohexane to cyclohexanol-on mixture, and methyl aromatic compounds (toluene, xylene) to the corresponding aromatic mon or di-carboxylic acids.[361]

The relevance of catalytic oxidations mediated by first-row transition metals to enzymic oxygen tions has stimulated considerable interest in creating biomimetic catalytic oxidation systems.[503,5] A list of the most representative systems is given in Table 7 together with their oxidizing propertie Some of these systems, particularly those using first-row metal porphyrins, are particularly effecti hydrocarbon oxidants, with a high selectivity, sometimes approaching that observed in enzym oxygenases.

Table 7 Oxidation of Hydrocarbons by Model Systems[a]

System	*Alkene epoxidation* S	*Alkene epoxidation* NS	*Alkane hydroxylation* S	*Alkane hydroxylation* NS	*Arene hydroxylation*	*Arene hydroxylation NIH shift*	*Alkene ketonization*	*Refs.*
In(TPP)Cl/PhIO	—	+	—	+	Low	—	—	478–480
In(TPP)Cl/O_2+H_2/Pt	+	—	+		—	—	—	481
In(TPP)Cl/Bu_4NBH_4/O_2	—	—	—	—	—	—	+	482
In(TPP)OAc/NaOCl/R_4NCl		+	—	—	—	—	—	483
In(TPP)Cl/ascorbate/O_2	+		+		—	—	—	484
Fe^{II}/H_2O_2(Fenton)	No		—	+	+	No	—	485–488
Fe(acac)$_3$/H_2O_2/MeCN	—	+	—	—	—	—	—	489
Fe^{II}/EDTA/ascorbate/O_2 (Undenfriend)	No		Low		+	No	—	490–492
Fe^{II}/*o*-mercaptobenzoate/O_2	No		—	+	+	No	—	488, 493, 494
Fe^{II}/hydrazobenzene/H^+/O_2	No		+		+		—	495
Fe^0/AcOH/py/H_2S	—	—	+		—	—	—	496
Fe(TPP)Cl/PhIO	+	—	+	—	Low	+	—	488, 497–499
Fe(TPP)Cl/*p*—CN—DMANO	+	—	Low		—	—	—	500
Fe(TPP)Cl/CHP	—	—	—	+	—	—	—	501
Co(TPP)/CHP	—	—	—	+	—	—	—	502

Abbreviations: *p*-CN—DMANO = *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide; CHP = cumyl hydroperoxide; S = stereoselective; NS = nonstereoselective.

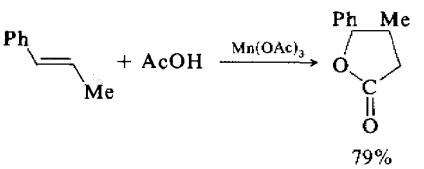
1.3.6.2 Manganese Catalysts

1.3.6.2.1 *Oxidation by manganese(III) salts*

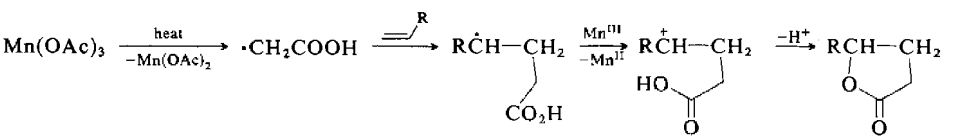
Owing to their lower oxidation-reduction potential, manganese(III) salts are weaker oxidants than cobalt(III) compounds. The reactivity of $Mn(OAc)_3$ towards hydrocarbons is strongly enhanced by the presence of strong acids or bromides.

i) Alkenes

The stoichiometric oxidation of alkenes by $Mn(OAc)_3$ in acetic acid at 120 °C affords γ-lactones in good yield, *via* the homolytic addition of carboxymethyl radical to the double bond (equations 204 and 205).[504–506]



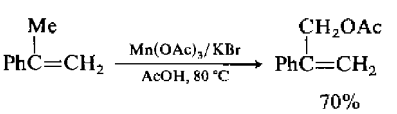
(204)



(205)

Under appropriate conditions, $Mn(OAc)_3$ can be used as a free-radical initiator for the homolytic addition of acetic anhydride to terminal alkenes. Linear or α-branched carboxylic acids can be produced in 70–80% yields based on α-alkenes.[507]

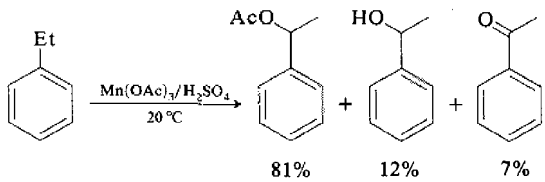
In the presence of bromide, the oxidation of alkenes by $Mn(OAc)_3$ in acetic acid readily occurs at 70–80 °C and produces allylic acetates in good yields. Thus cyclohexene is oxidized to cyclohexenyl acetate in 83% yield,[508] and α-methylstyrene to β-phenylallyl acetate in 70% yield,[509] with a mechanism involving allylic hydrogen abstraction by bromine atoms coming from the oxidation of bromide by Mn^{III} (equation 206).



(206)

(ii) Aromatic compounds

The oxidation of substituted aromatic hydrocarbons by $Mn(OAc)_3$ in refluxing acetic acid proceeds by two competing mechanisms: (a) a free radical addition of carboxymethyl radical to the nuclear ring, forming 2-arylacetic acids; and (b) a benzylic hydrogen abstraction by Mn^{III} resulting in the formation of benzyl acetates.[510,511] In the presence of strong acids such as sulfuric, trichloro- or trifluoro-acetic acids, only benzylic oxidation products are readily formed at room temperature (equation 207).[512,513]



(207)

(iii) Alkanes

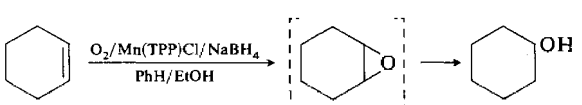
Manganese(III) acetate is poorly reactive with saturated hydrocarbons.[514] However, oxidation of adamantane by $Mn(OAc)_3$ in trifluoroacetic acid gives relatively high yields of 1-adamantyl trifluoroacetate, showing a preferential attack at tertiary C—H bonds.[515] Oxidation of *n*-alkanes by air in the presence of manganese catalysts constitutes the basis for an industrial process for the manufacture of synthetic fatty acids from *n*-alkanes of petroleum origin, which has been commercially developed in the Soviet Union.[516]

61.3.6.2.2 Catalysis by manganese porphyrins

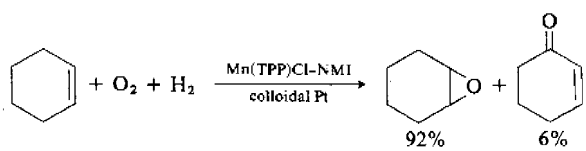
The ability of heme-containing cytochrome *P*-450 enzymes to catalyze the hydroxylation of hydrocarbons and the epoxidation of alkenes by O_2 in the presence of hydrogen-donor NADPH cofactor has stimulated the screening of synthetic metalloporphyrins for their oxidizing properties in the presence of various oxygen sources such as O_2+coreducing agents, iodosylbenzene or hypochlorites. Manganese-porphyrin complexes have recently been shown to possess many interesting properties as epoxidation and hydroxylation catalysts.

(i) Oxidation by dioxygen and coreducing agents

In 1979, Tabushi and coworkers reported that oxygenation of cyclohexene in the presence of Mn(TPP)Cl and sodium borohydride unusually produced cyclohexanol as the major product, while the same reaction carried out in the absence of $NaBH_4$ afforded the conventional radical autoxidation products. Since cyclohexene oxide was readily transformed into cyclohexanol under the reaction conditions, it was reasonably suggested that the epoxide is the primary product of the reaction (equation 208).[518] Later, the same authors were able to stop the reaction at the epoxide stage by using Mn(TPP)Cl, 1-methylimidazole (NMI), O_2 and (H_2+colloidal platinum) as the coreducing agent (equation 209).[481] Although a substantial amount of water was directly produced from the reaction of O_2+H_2, epoxide was catalytically formed with respect to manganese (65 turnovers) and platinum (300 turnovers). The reactivity order of alkenes, *i.e.* increasing with their nucleophilic nature, was found to be similar to that observed with a related Mn(TPP)Cl/PhIO catalytic epoxidation system (see below). However, in contrast to this PhIO system, the epoxidation of alkenes with O_2+H_2 proceeds with retention of configuration (*cis*-alkenes gave *cis*-epoxides only). The same catalytic system was also found to hydroxylate alkanes, but at a lower rate. The hydroxylation preferentially occurs at the tertiary C—H bonds, as shown by the formation of 1-adamantanol as the main product from adamantane.[481]

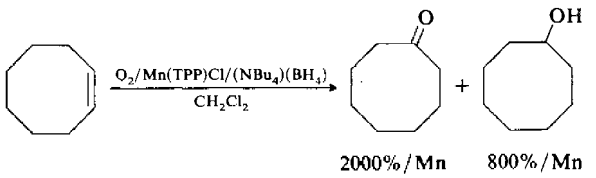


(208)



(209)

A surprisingly different oxidation of alkenes was found to occur in the presence of Mn(TPP)Cl catalyst and $[NBu_4][BH_4]$ coreducing agent.[482] Except for cyclohexene (transformed into cyclohex-en-3-ol and cyclohexanol), the other alkenes, *viz.* cyclooctene, styrene and 1-octene, were transformed into the corresponding ketone and the ensuing alcohol hydrogenation product (equation 210).



(210)

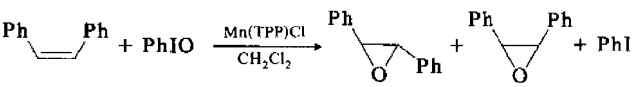
In the presence of ascorbate coreducing agent and under phase-transfer conditions, manganese porphyrins have recently been shown to activate oxygen by catalyzing epoxidation of alkenes and hydroxylation of alkanes to alkanol-one mixtures.[484]

(ii) Oxidation by iodosylbenzene

Iodosylbenzene has been extensively utilized over the last few years for its ability to cleanly transfer 'oxene' oxygen atoms to metals and possibly generate high-valent reactive metal-oxo species. PhIO has been successfully used instead of O_2 + NADPH in conjunction with cytochrome *P*-450 to hydroxylate alkanes,[81] and has found a variety of interesting applications as a two-electron oxidant in the presence of first-row transition metal porphyrins.

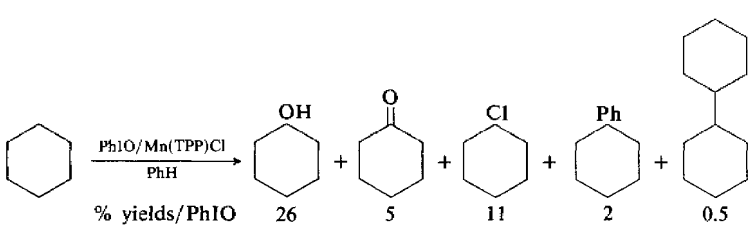
The oxidative properties of iodosylbenzene in the presence of Mn(TPP)Cl towards hydroxylation of alkanes[478,479] and epoxidation of alkenes[478] were simultaneously reported by Hill[479] and Groves.[478] These oxidations have the characteristics of a stepwise radical reaction.

(a) Alkenes are epoxidized with loss of stereochemistry at the double bond, as shown by the formation of a 1.6:1 mixture of *trans*- and *cis*-epoxides with an 88% overall yield (based on PhIO) from the oxidation of *cis*-stilbene (equation 211).[478] A major amount of *cis*-stilbene oxide was found in the presence of Mn(TTP)Cl (TTP = tetra-*o*-tolylporphyrin), showing that the product distribution is sensitive to the nature of the porphyrin ring. Epoxidation of norbornene in the presence of $[^{18}O]H_2O$ results in the formation of 80% labeled norbornene oxide, and suggests the intermediacy of a reactive high-valent manganese-oxo species.[478]



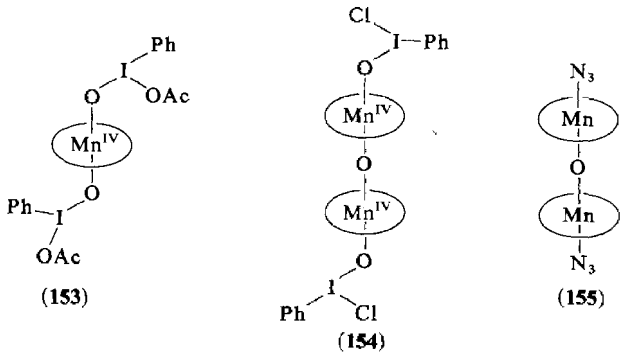
(211)

(b) Oxidation of alkanes (R—H) by PhIO in the presence of Mn(TPP)Cl results in the formation of alcohol and alkyl chloride along with minor amounts of coupling products R—R (equation 212).[479,519] Hydroxylation of alkanes preferentially occurs at the more nucleophilic tertiary C—H bonds. Oxidation of norcarane has all the characteristics of a radical reaction.[478]



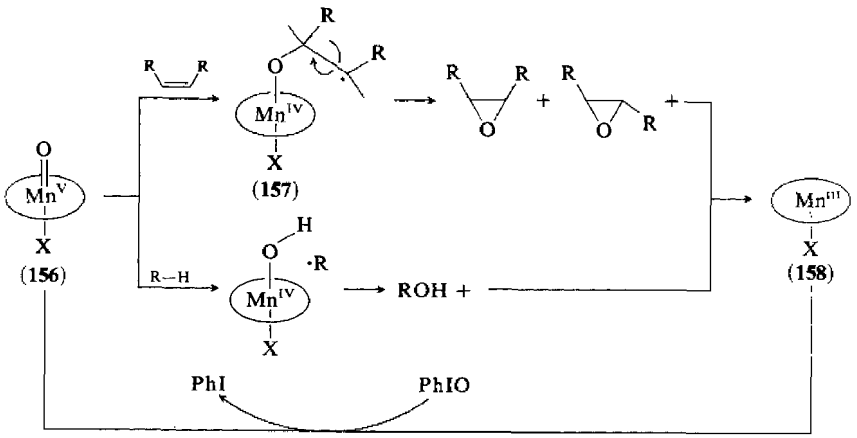
(212)

(c) Attempts to isolate the reactive intermediates from the reaction of PhIO with manganese-porphyrin precursors led to the characterization of Mn^{IV}–PhIO adducts with the presumed formula (**153**) [from Mn(TPP)OAc] and (**154**) [from Mn(TPP)Cl]. Reaction of $Mn(TPP)N_3$ with PhIO yielded the dinuclear μ-oxo complex (**155**), which has been characterized by an X-ray crystal structure.[520] Complexes (**153**) and (**154**) were found to epoxidize alkenes and to hydroxylate alkanes in the same way as in the catalytic reactions.[519] The μ-oxo compound (**155**) oxidizes PPh_3 to PPh_3O but is much less reactive than (**153**) and (**154**) toward alkanes.



(153) (154) (155)

(d) A likely mechanism which is consistent with the experimental data involves Mn^{V}-oxo species (**156**) generated from (**153**), (**154**) or (**155**) as the active intermediate. This intermediate (**156**) can either homolytically add to double bonds to give a free-rotating free-radical intermediate (**157**), which decomposes into a *cis*- + *trans*-epoxide mixture or abstract hydrogen atoms from alkanes to give a free radical R· with subsequent formation of alcohol in the cage species (**158**) (Scheme 12).[478-480,519]



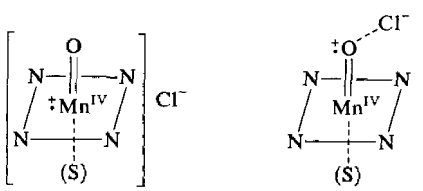
Scheme 12

(iii) Epoxidation of alkenes by sodium hypochlorite

An interesting epoxidation reaction of synthetic interest has recently been reported by Meunier and coworkers.[483] The reaction of sodium hypochlorite with styrene catalyzed by Mn(TPP)X (X = Cl, OAc) under phase-transfer conditions affords styrene oxide in high yield (equation 213).

$$PhCH{=}CH_2 + NaOCl \xrightarrow[CH_2Cl_2/H_2O]{Mn(TPP)X/R_4NCl} PhCH\!\!\underset{O}{\diagup\!\diagdown}\!\!CH_2 + NaCl \qquad (213)$$

Addition of pyridine bases to the catalytic system caused a considerable increase in the rate and selectivity of the reaction, reaching 80% yield of styrene oxide for 100% styrene conversion (r.t., 30 min). In the presence of this pyridine-modified system, the reactivity of alkenes is in the order styrene > trisubstituted > *cis*-disubstituted > *trans*-disubstituted > monosubstituted. The epoxidation of alkenes is not stereoselective. In the absence of pyridine, *cis*-stilbene was converted into a 1.8:1 *trans*:*cis* epoxide mixture, whereas the *cis* isomer prevails in the presence of excess pyridine ligands. Neither chlorohydrins nor pyridine *N*-oxides are involved in this catalytic system. Attempts to isolate the reactive intermediate led to the characterization of a relatively stable



(**159a**) Oxo radical cation (**159b**) Oxo-like

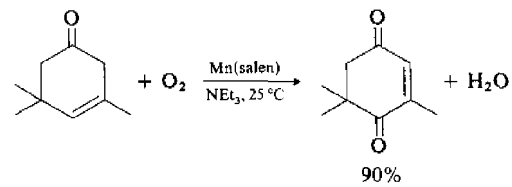
manganese(IV) complex with the formula Mn(TMP)OCl (**159**) (TMP = tetramesitylporphyrin) for which the oxo radical cation (**159a**) or the oxo-type structure (**159b**) was suggested.[521] This complex (**159**) was found to epoxidize styrene both stoichiometrically and catalytically in the presence of NaOCl.

Anchoring Mn(TPP)OAc to a rigid polyisocyanide support has resulted in a considerable increase in the epoxidation rate of cyclohexene by NaOCl. These solid catalysts can be recovered and retain their activity during several consecutive experiments.[522]

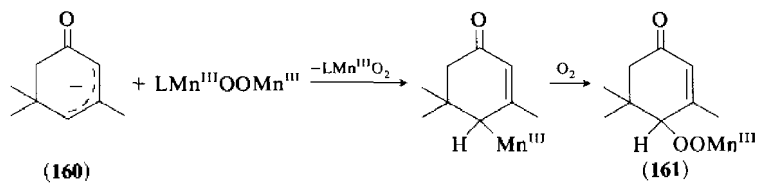
61.3.6.2.3 Miscellaneous manganese-catalyzed oxidations

Catalytic oxidations using manganese complexes and dioxygen or peroxide oxidants are rather rare. Although reversible dioxygen adducts of the superoxo or peroxo type have been detected in the interaction of manganese(II)-pophyrin or -Schiff base complexes with O_2 at low temperature,[10] or from the reaction of $MnX_2(PR_3)$ (X = Cl, Br, I) with oxygen,[523] no reactivity towards hydrocarbons has been reported.

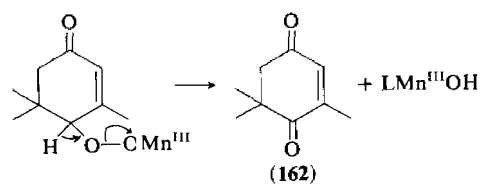
β-Isophorone can be cleanly oxidized by air to 1,5,5-trimethylcyclohexene-3,6-dione in the presence of Mn(salen) and triethylamine (equation 214).[524] The mechanism suggested involves carbanion (**160**) formation from the reaction of NEt_3 with β-isophorone, followed by the formation of an alkyl peroxide-manganese(III) complex (**161**) which decomposes to the dienone (**162**).[524,56]



(214)



(160) (161)



(162)

(215)

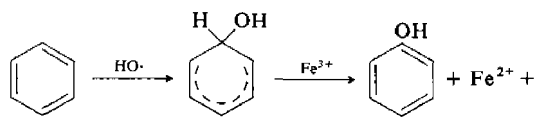
61.3.6.3 Iron Catalysts

61.3.6.3.1 Oxidation by peroxides

The hydroxylating properties of hydrogen peroxide in the presence of iron(II) salts have been known since 1894.[485] This system, known as Fenton's reagent, has been widely used as an effective oxidant of a great variety of organic substrates.[486–488,525–526] A widely accepted mechanism, proposed by Haber and Weiss, involves the formation of hydroxyl radicals from the cleavage of the peroxide bond by iron(II) ions (equation 216).[527]

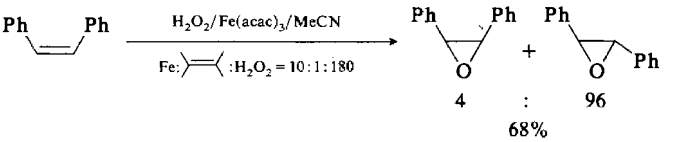
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + HO\cdot \qquad (216)$$

Fenton's reagent hydroxylates aromatic rings, generally with low yields, at the more nucleophilic carbon positions, and gives substantial amounts of biaryl by-products resulting from the dimerization of intermediate radical species (equation 217).[491]



(217)

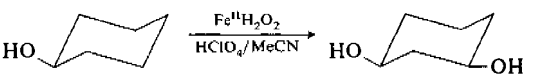
The use of Fenton's reagent in nonprotic solvents (MeCN, CH_2Cl_2) results in substantial changes in the reactivity and the selectivity of the transformations. Thus alkenes are stoichiometrically epoxidized in a nonstereoselective fashion by $H_2O_2/Fe(acac)_3$ in acetonitrile (equation 218).[489,528]



(218)

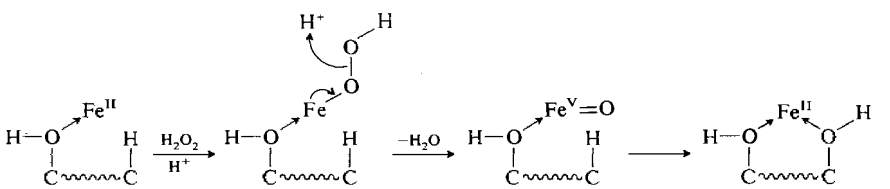
However, the same catalytic system did not hydroxylate aromatic compounds in a way significantly different from usual aqueous Fenton's reagents.[529]

Oxidation of cyclohexanol by H_2O_2 in the presence of $Fe(ClO_4)_2$ and perchloric acid in acetonitrile was found to give cyclohexanone and the six possible cyclohexanediols in which *cis*-1,3-cyclohexanediol represented 72% of the total amount of diols produced.[530] This unusual regioselectivity was explained by the formation of a ferryl ion species FeO^{2+} or $Fe^{IV}=O$ by heterolysis of the hydroperoxo compound capable of abstracting the *cis* hydrogen atom at carbon 3 (equations 219 and 220).[530] Several Fenton's reagents modified by the addition of catechol[531,533,534] or quinones[532] have been shown to give increased yields and selectivities in the hydroxylation of aromatic hydrocarbons.



72% regiospecificity

(219)



(220)

61.3.6.3.2 Oxidation by dioxygen and a coreducing agent

Several biomimetic systems containing iron catalysts and a coreducing agent have been found to hydroxylate hydrocarbons by dioxygen under mild conditions (equation 221).[12,503,526,535] The first of these hydroxylating systems was described by Undenfriend[490] and involves Fe^{II}(EDTA) as the catalyst and ascorbic acid as the coreducing agent. This reagent was found to hydroxylate arenes to phenols, and alkanes to alcohols.[491,492] Several related systems using other coreducing agents such as diaminopurine,[536] 2-mercaptobenzoic acid,[493] hydrazobenzene,[495] 2-mercaptoethanol[537] and metallic iron powder[538,496] have also been used, and these oxidizing properties are listed in Table 7. The yields in oxidation products are generally proportional to the concentration of the coreducing agent, but are much lower than those expected from reaction (221), since parallel oxidation of the coreducing agent occurs. An accurate comparison of the oxidizing properties of these model systems is difficult to make. However, these systems differ both from cytochrome *P*-450 and from PhIO/iron porphyrin reagents, and have more or less electrophilic properties depending on the nature of the coreducing agent.

$$RH + DH_2 + O_2 \xrightarrow{(Fe)} ROH + D + H_2O \qquad (221)$$

(a) Hydroxylation of alkanes preferentially occurs at the more nucleophilic tertiary C—H positions, but some of these systems using 2-mercaptoethanol[537] or metallic iron powder[496] hydroxylate adamantane with preference for the secondary position. However, none of these systems hydroxylates *cis*-decalin with retention of configuration at the hydroxylated atom.[488]

(b) Hydroxylation of aromatic hydrocarbons by these model systems generally occurs at the more nucleophilic ring carbon atoms, but none of these systems gives any significant NIH shift during the hydroxylation.

(c) Epoxidation of alkenes does not occur to a significant extent with these model systems, and allylic hydroxylation is the main reaction observed.

(d) Oxidative demethylation of anisole occurs with a low kinetic isotope effect, in contrast to cytochrome P-450 and PhIO/Fe(TPP)Cl.[539]

No simple picture has emerged concerning the mechanism of these oxidations. In one rationale, dioxygen is reduced to hydrogen peroxide by the coreducing agent, and hydroxylation is performed by hydroxyl radicals as with Fenton's reagent.[491] Further proposals involve superoxide $Fe^{III}-O-O^{\cdot}$,[494] hydroperoxide $Fe^{III}-OOH$,[495] oxenoid $Fe^{III}-O-O^{-}$ [71,540] or ferryl ion FeO^{2+} (or $Fe^{IV}=O$)[54] as the active oxidant. Recent studies by Barton and coworkers concern the hydroxylating properties of the $Fe^0/RCOOH/py-H_2O/O_2$ system which exhibits particular selectivity towards secondary C—H bonds of alkanes.[496] Since sulfides are not oxidized to sulfoxides by this catalytic system, it has been assumed that the active species is neither a radical nor 'oxenoid' reagent, but may be a coordinatively unsaturated iron complex capable of activating alkanes by insertion between C—H bonds.[496]

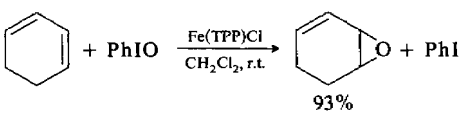
61.3.6.3.3 Catalysis by iron porphyrins

(i) Oxidation by iodosylbenzene

Epoxidation of alkenes and hydroxylation of alkanes can be achieved under mild conditions with iron porphyrin catalysts and iodosylbenzene as the oxidant.[497–499,488]

(1) Epoxidation of alkenes has the following characteristics.[497,498,488]

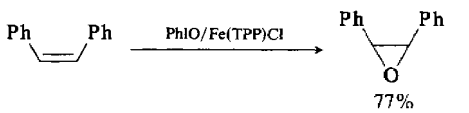
(a) The reactivity of alkenes increases with increasing alkyl substitution at the double bonds in the following order: tetramethylethylene : 2-methylbut-2-ene : cyclohexene : oct-1-ene = 204 : 76 : 20 : 1.[488,498] High yields of epoxide based on the iodosylbenzene consumed are obtained with electron-rich alkenes. 1,3-Cyclohexadiene is oxidized to the corresponding monoepoxide in 93% yield (equation 222).[498]



93% (222)

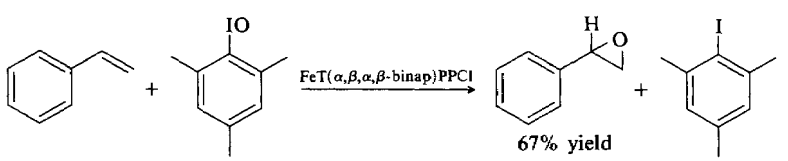
(b) *cis*-Alkenes are much more reactive than *trans* isomers.[498,488] Thus epoxidation of *cis*-stilbene or *cis*-4-methylpentene in the presence of Fe(TPP)Cl is at least 14 times faster than that of the *trans* analogs, in contrast to epoxidation by peracids. The relative reactivity of the *cis*- and *trans*-alkenes is sensitive to the substitution on the porphyrin periphery, and the reaction becomes more selective for *cis*-alkenes as the steric bulk of the porphyrin increases.

(c) In contrast to the PhIO/Mn(TPP)Cl system, epoxidation of alkenes occurs with high retention of configuration. *cis*-Alkenes are almost exclusively converted to *cis*-epoxides. Norbornene is transformed into a 67 : 3 mixture of *exo*- and *endo*-norbornene oxide (*e.g.* equation 223).[498]



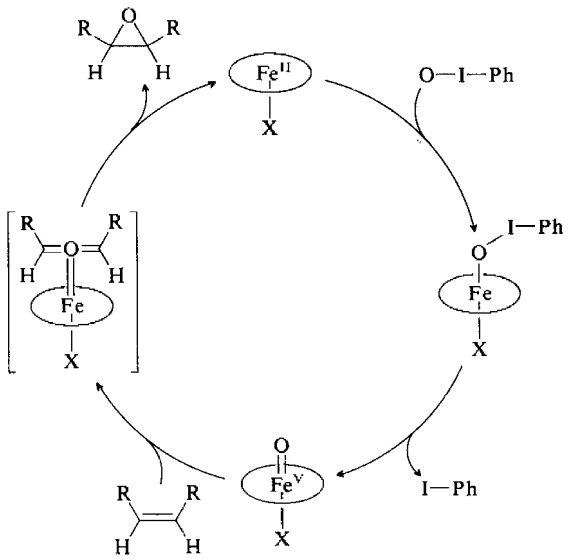
77% (223)

(d) Asymmetric epoxidation of prochiral alkenes can be performed by PhIO in the presence of chiral iron porphyrins.[541] Thus styrene was epoxidized to (*R*)-(+)-styrene oxide in 67% chemical yield and 48% e.e. in the presence of iodosylmesitylene and FeT($\alpha,\beta,\alpha,\beta$-binap)PPCl [$\alpha,\beta,\alpha,\beta$-binap = 5$\alpha$,10$\beta$,15$\alpha$,20$\beta$-tetrakis(O-[(*S*)-2′-carboxymethyl-1,1′-binaphthyl-2-carboxamido]phenyl)porphyrin] (equation 224).[541]



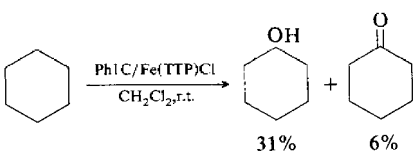
67% yield
48% e.e. (224)

(e) The proposed epoxidation mechanism depicted in Scheme 13 involves oxygen transfer from a reactive iron(V)-oxo intermediate to the alkene. The approach of the alkene to the iron-bound oxygen presumably occurs 'side-on' and parallel to the porphyrin plane, and involves the interaction of partially filled oxygen-iron $p\pi$–$d\pi$ antibonding orbitals.

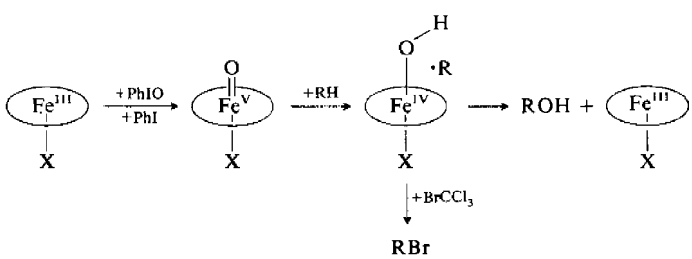


Scheme 13

(2) Oxidation of alkanes by PhIO in the presence of iron(III) porphyrins at room temperature results in the formation of alcohol as the major product along with consecutive carbonyl oxidation products (equation 225).[498,488,502] Hydroxylation of *cis*-decalin occurs with retention of configuration at C-9 and mainly produces *cis*-9-decalol.[498,488] Oxidation of *n*-heptane results in the formation of 2-, 3- and 4-heptanols with an overall yield of *ca.* 20% based on PhIO. The heptanol distribution depends on the nature of the porphyrin ligand, and ω-1-hydroxylation increases as the iron accessibility of the catalyst decreases.[502] Carbon radical intermediates were revealed by the formation of larger amounts of bromocycloheptane when the hydroxylation of cycloheptane was carried out in the presence of CCl_3Br.[498] The hydrogen isotope effect for cyclohexane hydroxylation by Fe(TTP)Cl was found to be 12.9 ± 1. The proposed hydroxylation mechanism involves hydrogen atom abstraction from the alkane by the reactive $Fe^{V}{=}O$ intermediate, and rapid collapse of this radical to give the product alcohol and to regenerate the Fe^{III} catalyst (equation 226).[498]



(225)



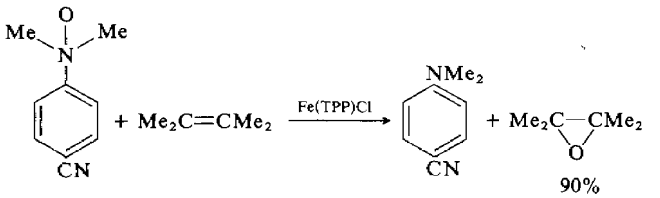
(226)

(3) In contrast to cytochrome *P*-450 and iron-based models using O_2 and a coreducing agent, iron porphyrins are poor catalysts for the hydroxylation by PhIO of aromatic hydrocarbons at the ring positions.[488,499] Benzene is not oxidized, and toluene gives mainly benzylic oxidation products, *i.e.* benzyl alcohol and benzaldehyde. However, high NIH shift values (60–70%) were observed in the hydroxylation of [4-^{2}H]anisole and [1,4-$^2H_2$]naphthalene by PhIO in the presence of Fe(TPP)Cl and Fe(TFPP)Cl [TFPP = tetra(pentafluorophenyl)porphyrin].[488,499]

(ii) Oxidation by miscellaneous oxidants

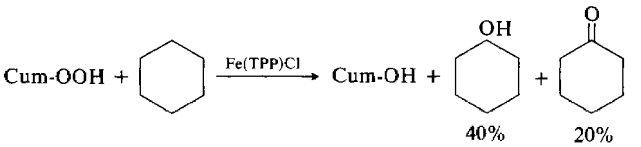
Tertiary amine oxides can be used instead of iodosylbenzene for the epoxidation of alkenes in the presence of Fe(TPP)Cl.[500] *p*-Cyano-*N*,*N*-dimethylaniline *N*-oxide (*p*-CN-DMANO) has

oxidizing properties similar to PhIO and provides the same products. The major difference between these two oxidants is that while PhIO is both stereospecific and kinetically selective for *cis*-alkenes, *p*-CN-DMANO is only stereospecific and also reacts with *trans*-alkenes (equation 227).

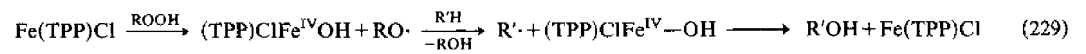


(227)

Hydroxylation of alkanes can be performed by TBHP or cumyl hydroperoxide in the presence of iron porphyrin catalysts.[501,502] The characteristics of this reaction are very different from PhIO/Fe(TPP) systems. No epoxidation of alkenes occurs, and the alcohol distribution is completely independent of the nature of the iron porphyrin used (equation 228). A 'Fenton-type' mechanism involving active species not including the metal has been suggested (equation 229).

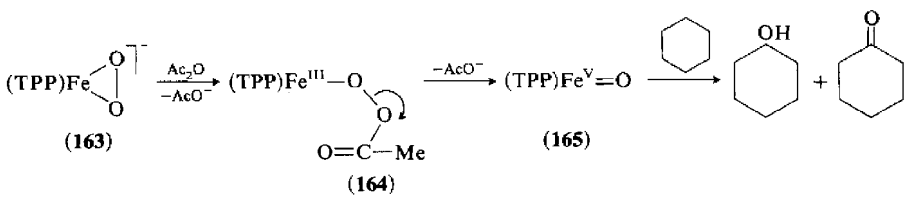


(228)



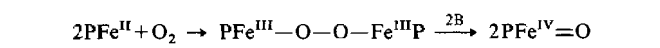
(229)

The porphyrin-iron(III)-peroxo complex $[Fe(TPP)O_2]$ (**163**) was prepared by the reaction of KO_2 with $Fe^{II}(TPP)$ in the presence of a crown ether, and characterized by spectroscopic methods [$\nu(O—O) = 806\ cm^{-1}$][542]. This peroxo complex (**163**) was found to be inactive toward hydrocarbons. However, addition of excess acetic anhydride to (**163**) dissolved in a benzene–cyclohexane mixture results in the formation of cyclohexanol and cyclohexanone. This reaction is thought to proceed *via* acylation of the peroxo group, giving iron percarboxylate (**164**), which decomposes to an Fe^{V}-oxo compound (**165**) capable of hydroxylating alkanes.[543] Such a mechanism has been suggested for the hydroxylation of camphor by *Pseudomonas* cytochrome *P*-450.[544]



(230)

Low-spin iron^{IV}-oxo-porphyrin complexes such as (NMeIm)(TPP)Fe^{IV}=O can be obtained from the homolytic dissociation of the dinuclear Fe^{III}-μ-peroxo complex in the presence of bases (B) (equation 231).[545] However, this iron(IV)-oxo complex was only found to oxidize phosphines to phosphine oxides.[545] Hence, although there is strong evidence for the involvement of high-valent reactive iron-oxo species in oxidations by iodosylbenzene and possibly in oxidations by cytochrome *P*-450, the lack of structural data for these reactive intermediates raises some doubt concerning the nature and the metal valency of these reactive species. The difference in reactivity of iodosylbenzene, on the one hand, and of peroxide or O_2 + coreductant, on the other, makes it difficult to propose single reactive intermediates. Furthermore, the hydroxylating and epoxidizing properties of vanadium and chromium peroxides also give some consistency to the involvement of iron peroxide species, or related iron-iodosylbenzene or -hypochlorite adducts as reactive intermediates. There is no doubt that the intensive efforts devoted to this subject will shed some light in the near future on the mechanism of these fascinating oxidation reactions.

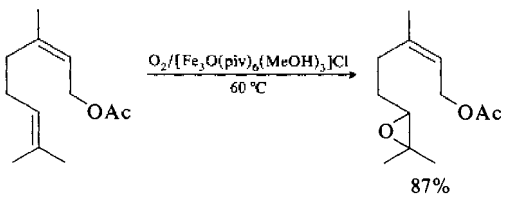


(231)

61.3.6.3.4 Miscellaneous oxidations

μ_3-Oxo-triiron complexes $[Fe_3O(RCO_2)_6L_3]X$ [R = Me, Bu^t(piv); L = MeOH, Py; X = Cl, OAc] have recently been shown to catalyze the epoxidation of alkenyl acetate by molecular oxygen

under mild conditions (60 °C, 1 atm) (equation 232).[546] The regiospecificity of this reaction resembles that of peracid epoxidation but is opposite to that of $Bu^tOOH/VO(acac)_2$. Alkenyl acetates were found to be the best substrates for this reagent. Simple alkenes are much less efficiently epoxidized. The reaction is not stereospecific, as shown by the formation of a 5:1 mixture of *trans*- and *cis*-epoxides from the oxidation of *cis*-β-methylstyrene. One mole of dioxygen was consumed per mole of epoxide produced. This is twice the amount required for the stoichiometry of the reaction, and the detected oxidative degradation products account for one oxygen atom of O_2 not found in the epoxide product.[546] It is noteworthy that a similar μ_3-oxo-iron cluster $Fe_3O(AcO)_6(py)_3$ has been isolated from the reaction of iron powder with acetic acid in aqueous pyridine in air, a system which had previously been shown to hydroxylate alkanes.[496]



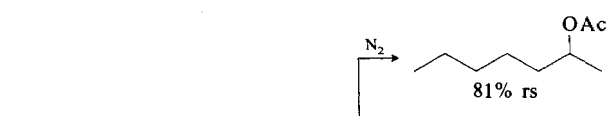
(232)

61.3.6.4 Cobalt Catalysts

61.3.6.4.1 Oxidation by cobalt(III) salts

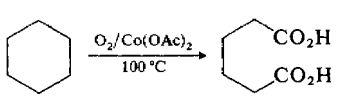
The oxidation of hydrocarbons by cobalt(III) acetate has been thoroughly investigated, due to its relevance to industrial homolytic oxidation processes.[56,361,547] Radical intermediates are produced from one-electron oxidation of hydrocarbons according to an electron transfer or an electrophilic substitution mechanism previously described in equations (200)–(203). These oxidations are dramatically accelerated by the presence of strong acids or halide salts.

Oxidation of *n*-alkanes by Co^{III} acetate in acetic acid occurs with a remarkable regioselectivity (rs) at the ω-1 position, giving 2-alkyl acetate as the major product in anaerobic conditions, and 2-alkanone in the presence of oxygen (equations 233 and 234).[548] Cyclohexane is readily oxidized in nitrogen by $Co(OAc)_3$ in acetic acid to mainly cyclohexyl acetate and 2-acetoxycyclohexanone.[549,550] In the presence of oxygen and a high cobalt concentration, adipic acid is the major product formed (equation 235).[551] Oxidation of adamantane by $Co(OAc)_3$ and TFA in AcOH preferentially occurs at the tertiary positions, producing 1-adamantyl acetate as the major product.[550]



(233)

(234)

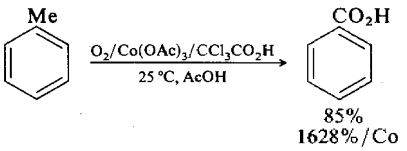


(235)

Oxidation of alkenes by $Co(OAc)_3$ preferentially occurs at the allylic positions, yielding 2-alkenyl acetate. Oxidation of cyclohexene by $Co(OAc)_3$ and TFA in AcOH results in the formation of cyclohexenyl acetate along with minor amounts of the corresponding allyl alcohol.[550] The oxidation of ethylene by $Co(TFA)_3$ in TFA affords ethylene glycol bis(trifluoroacetate).[552]

Oxidation of alkylbenzene by $Co(OAc)_3$ mainly occurs at the side-chain benzylic positions, without formation of nuclear adducts. In nitrogen, benzylic acetates predominate, whereas aromatic acids are favored when oxygen is present.[512] Thus toluene is transformed into benzyl acetate and benzaldehyde by $Co(OAc)_3$ in AcOH under anerobic conditions.[553] When this reaction is

carried out in the presence of O_2 and trichloracetic acid, benzoic acid is almost exclusively formed with relatively high turnover numbers (equation 236).[512]



(236)

Halide salts also have a pronounced synergistic effect on the cobalt-catalyzed autoxidation of alkyl aromatic compounds to acids, which is of considerable industrial importance (see below).[56] For example, *p*-xylene is selectively converted to terephthalic acid by O_2 in the presence of $Co(OAc)_3$ and NaBr at 60 °C and atmospheric pressure. Oxidation of bromide by Co^{III} produces bromine atoms, which act as chain-transfer agents (equation 237 and 238).[56] When cobalt(II) acetate is used, long induction periods corresponding to the oxidation of Co^{II} to Co^{III} are observed. These induction periods can be eliminated by initiators such as TBHP or ozone. The oxidation of $Co(OAc)_2$ by ozone produces a μ_3-oxo-bridged trimer $Co_3O(OAc)_6(AcOH)_3$, which is itself a good initiator.[554] This trimeric complex forms spectrophotometrically characterized charge-transfer complexes with a variety of aromatic hydrocarbons.[554] This may be of significant importance for the initiation mechanism of Co^{III}-catalyzed oxidations.[554]

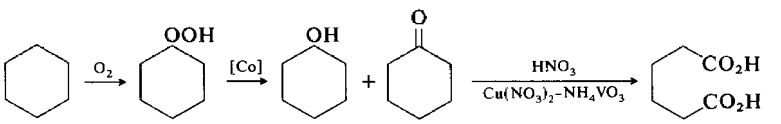
$$Co(OAc)_3 + Br^- \xrightarrow[-AcO^-]{} Co(OAc)_2Br \longrightarrow Co(OAc)_2 + Br\cdot \quad (237)$$

$$Br\cdot + ArMe \xrightarrow[-HBr]{} ArCH_2\cdot \xrightarrow{O_2} ArCH_2O_2\cdot \xrightarrow{Co(OAc)_2} ArCHO + Co(OAc)_2OH \xrightarrow{O_2} ArCO_2H \quad (238)$$

61.3.6.4.2 Industrially important cobalt-catalyzed oxidation of hydrocarbons

(i) Adipic acid from cyclohexane

Adipic acid is a most important petrochemical product which is mostly used for the synthesis of nylon 6.6 from its condensation with hexamethylenediamine. Cyclohexane is transformed to adipic acid in two steps: (a) oxidation of cyclohexane to a cyclohexanol-cyclohexanone mixture (ol-one) *via* the formation of cyclohexyl hydroperoxide followed by (b) oxidation of the ol-one mixture to adipic acid by nitric acid (equation 239).



(239)

In the Dupont process, cyclohexane is reacted with air at 150 °C and 10 atm pressure in the presence of a soluble cobalt(II) salt (naphthenate or stearate). The conversion is limited to 8–10% in order to prevent consecutive oxidation of the ol-one mixture. Nonconverted cyclohexane is recycled to the oxidation reactor. Combined yields of ol-one mixture are 70–80%.[83,84,555] The ol-one mixture is sent to another oxidation reactor where oxidation by nitric acid is performed at 70–80 °C by nitric acid (45–50%) in the presence of a mixture of $Cu(NO_3)_2$ and NH_4VO_3 catalysts, which increase the selectivity of the reaction. The reaction is complete in a few minutes and adipic acid precipitates from the reaction medium. The adipic acid yield is about 90%. Nitric acid oxidation produces gaseous products, mainly nitric oxides, which are recycled to a nitric acid synthesis unit. Some nitric acid is lost to products such as N_2 and N_2O which are not recovered.

In a modified version developed by Scientific Design, the autoxidation of cyclohexane is carried out in the presence of boric acid which forms boric esters with cyclohexanol and cyclohexyl hydroperoxide. Boric esters such as $B(OC_6H_{11})_3$ are hydrolyzed to cyclohexanol and cyclohexanone. The resulting boric acid is dehydrated and recycled. This method produces an approximately 10:1 ol:one mixture, with an overall yield of 90% for a cyclohexane conversion of 10%. Although this process gives higher yields of ol-one mixture, it requires added investments and operating costs for boric acid recycling.[83,84]

A similar procedure has been developed by Chemische Werke Hulls for the oxidation of cyclododecane to a cyclododecanol-one mixture by air in the presence of boric acid with trace amounts of cobalt(II) carboxylate at 160–180 °C and 1–3 atm.[556] The ol-one mixture (5:1) is

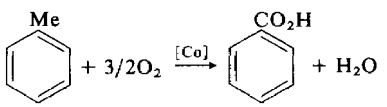
produced in *ca.* 80% yield at 33% conversion. Further oxidation of cyclododecanol–one by nitric acid affords dodecanedioic acid, a most important intermediate for the synthesis of polyamides (nylon 12) for several specialty applications.

(ii) Acetic acid from butane

Butane from natural gas is cheap and abundant in the United States, where it is used as an important feedstock for the synthesis of acetic acid. Since acetic acid is the most stable oxidation product from butane, the transformation is carried out at high butane conversions. In the industrial processes (Celanese, Hüls), butane is oxidized by air in an acetic acid solution containing a cobalt catalyst (stearate, naphthenate) at 180–190 °C and 50–70 atm.[361,557] The AcOH yield is about 40–45% for *ca.* 30% butane conversion. By-products include CO_2 and formic, propionic and succinic acids, which are vaporized. The other by-products are recycled for acetic acid synthesis. Light naphthas can be used instead of butane as acetic adic feedstock, and are oxidized under similar conditions in Europe where natural gas is less abundant (Distillers and BP processes). Acetic acid can also be obtained with much higher selectivity (95–97%) from the oxidation of acetaldehyde by air at 60 °C and atmospheric pressure in an acetic acid solution and in the presence of cobalt acetate.[361,558]

(iii) Benzoic acid from toluene

Benzoic acid is an important chemical intermediate which can also be used as a phenol precursor by decarbonylation in the presence of copper catalysts (Lummus process). It is produced industrially by oxidation of toluene by air in the presence of cobalt catalysts (Dow and Amoco processes; equation 240). The reaction can be carried out without solvent, or in an acetic acid solvent. The oxidation of toluene without solvent uses a cobalt octoate catalyst and operates at higher temperature (180–200 °C). Yields of benzoic acid are about 80% for *ca.* 50% toluene conversion.[361] In an acetic acid solution and in the presence of cobalt acetate, the reaction occurs at lower temperature conditions (110–120 °C) and gives higher yields in benzoic acid (90%).[83,84]



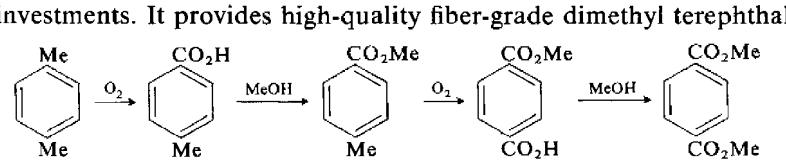
(240)

(iv) Terephthalic acid from p-xylene

This is one of the most important industrial oxidation processes. Terephthalic acid (TPA) is mostly used for the manufacture of polyester fibers, films and plastics, and its world production capacity reaches 8 Mt/year. Two major processes have been developed. The Amoco-Mid Century process produces terephthalic acid by the one-step oxidation of *p*-xylene in acetic acid, whereas the Dynamit Nobel process yields dimethyl terephthalate in several steps and in the absence of solvent.[83,84,86]

In the Amoco process, *p*-xylene is oxidized at 200 °C under 15–20 atm in acetic acid and in the presence of a catalyst consisting of a mixture of cobalt acetate (5% weight of the solution), manganese acetate (1%) and ammonium bromide. Owing to the highly corrosive nature of the reaction mixture, special titanium reactor vessels are required. One of the main difficulties of this process is to remove the intermediate oxidation products such as *p*-toluic acid or *p*-carboxybenzaldehyde which contaminate TPA obtained by precipitation from the reaction medium. A series of recrystallization and solvent extraction apparatus is required to obtain fiber grade TPA with 99.95% purity. The overall yield in TPA is *ca.* 90% for a 95% conversion of *p*-xylene.

The Dynamit Nobel process produces dimethyl terephthalate (DMT) by a complicated series of oxidation and esterification stages (equation 241).[83,84,86] In the oxidation section, *p*-xylene is oxidized at 150 °C and 6 atm without solvent and in the presence of cobalt octoate to TPA and *p*-toluic acid. These oxidation products are sent to another reactor for esterification by methanol at 250 °C and 30 atm. Fiber grade DMT is purified by several recrystallizations, and monoesters are recycled to the oxidation reactor. The overall yield in DMT is about 80%, which is lower than in the Amoco process. However, this process is competitive because it is not corrosive and requires lower investments. It provides high-quality fiber-grade dimethyl terephthalate.

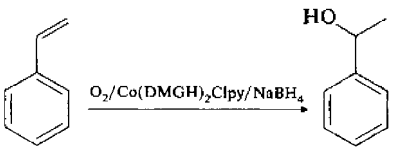


(241)

61.3.6.4.3 Catalysis by cobalt porphyrins and Schiff base complexes

(i) Oxidation of terminal alkenes by dioxygen and a coreducing agent

Styrene derivatives can be selectively converted to the corresponding benzyl alcohols by molecular oxygen in the presence of bis(dimethylglyoximato)chloro(pyridine)cobalt(III) and sodium tetrahydroborate (equation 242).[559] A likely mechanism for this reaction involves insertion of the alkene into the cobalt-hydride bond, followed by O_2 insertion into the cobalt-carbon bond, as in equation (11), and decomposition of the peroxide adduct (**168**) to the ketone, which is reduced to alcohol by $NaBH_4$ (equation 243).



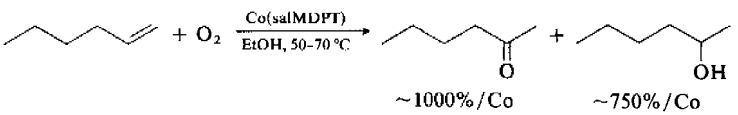
(242)

$$LnCo^{3+}-Cl \xrightarrow[-Cl^-]{NaBH_4} LnCo-H \xrightarrow{\overset{R}{=}} LnCo-\underset{\displaystyle R}{\underset{|}{C}}HMe \xrightarrow{O_2}$$

$$LnCo-O-O-\underset{\displaystyle R}{\underset{|}{\overset{\displaystyle H}{\overset{|}{C}}}}Me \xrightarrow{-LnCo-OH} R-\underset{\displaystyle O}{\underset{\|}{C}}-Me \xrightarrow{NaBH_4} R-\underset{\displaystyle H}{\underset{|}{\overset{\displaystyle OH}{\overset{|}{C}}}}-Me \qquad (243)$$

(**168**)

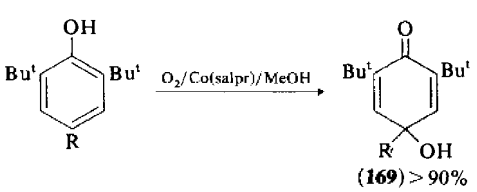
A somewhat similar oxidation of terminal alkenes to methyl ketone and alcohol by O_2 in the presence of Co(salMDPT) [salMDPT = bis(salicylideneiminopropyl)methylamine] and in ethanol solvent has recently been reported by Drago and coworkers (equation 244).[560] Only terminal alkenes were found to be reactive with this catalytic system. The reaction is alcohol dependent and occurs in ethanol and methanol but not in *t*-butyl or isopropyl alcohols. The alcohol is concomitantly oxidized during the reaction, and may act as a coreducing agent and/or favor the formation of cobalt hydride. This oxidation might occur according to the mechanism of equation (243).



(244)

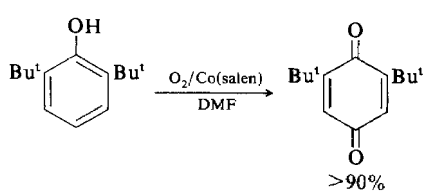
(ii) Oxidation of phenols

Cobalt-Schiff base complexes catalyze the selective oxidation of phenols by dioxygen into quinols (equation 245[561]) or quinones (equations 246[562,563] and 247[561]) under mild conditions.



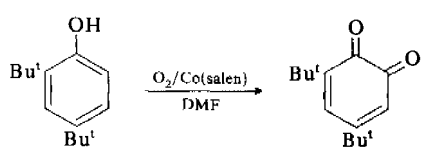
(**169**) > 90%

(245)



>90%

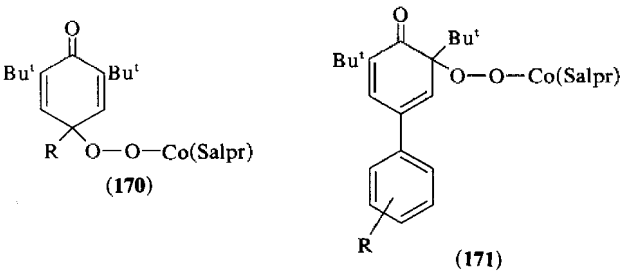
(246)



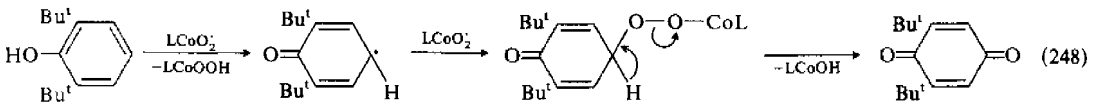
>85%

(247)

Nishinaga and co-workers isolated a series of stable cobalt(III)-alkyl peroxide complexes such as (**170**) and (**171**) in high yields from the reaction of the pentacoordinated Co^{II}-Schiff base complex with the corresponding phenol and O_2 in CH_2Cl_2.[564] Complex (**170**; R=Bu^t) has been characterized by an X-ray structure. These alkyl peroxide complexes presumably result from the homolytic addition of the superoxo complex $Co^{III}—O_2^{\cdot}$ to the phenoxide radical obtained by hydrogen abstraction from the phenolic substrate by the Co^{III}-superoxo complex. The quinone product results from β-hydride elimination from the alkyl peroxide complex (**172**)[561,56,565,566] The quinol (**169**) produced by equation (245) has been shown to result from the reduction of the Co^{III}-alkyl peroxide complex (**170**) by the solvent alcohol which is transformed into the corresponding carbonyl compound (equation 248).[561]



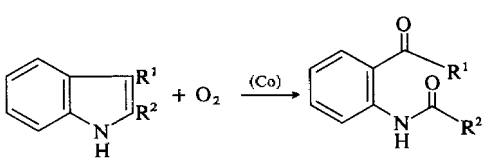
(**170**) (**171**)



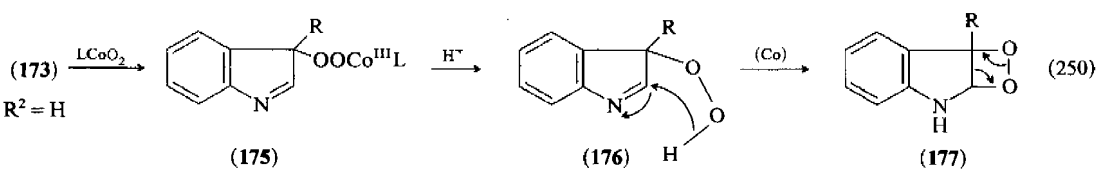
(**172**) (248)

(iii) Oxidative cleavage reactions

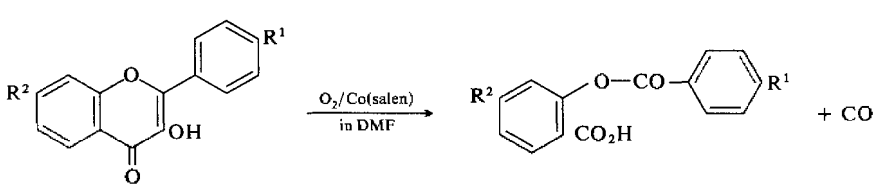
Cobalt^{II}-Schiff base complexes, *e.g.* Co(salen),[567] Co(acacen)[568] and cobalt(II) porphyrins,[569] *e.g.* Co(TPP), are effective catalysts for the selective oxygenation of 3-substituted indoles to keto amides (equation 249), a reaction which can be considered as a model for the heme-containing enzyme tryptophan-2,3-dioxygenase (equation 21).[66] This reaction has been shown to proceed *via* a ternary complex, Co-O_2-indole, with probable structure (**175**), which is converted into indolenyl hydroperoxide (**176**). Decomposition of (**176**) to the keto amide (**174**) readily occurs in the presence of Co(TPP), presumably *via* formation of a dioxetane intermediate (**177**).[569,56] Catalytic oxygenolysis of flavonols readily occurs in the presence of Co(salen) and involves a loss of one mole of CO (equation 251).[570]



(**173**) (**174**) (249)



(**175**) (**176**) (**177**) (250)

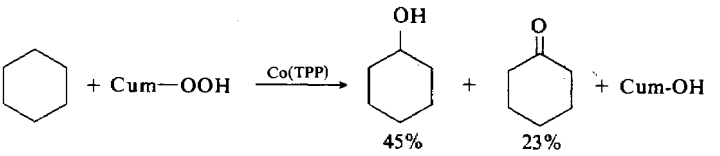


(251)

(iv) Hydroxylation of alkanes

Cobalt porphyrins catalyze the hydroxylation of cyclohexane by cumyl or *t*-butyl hydroperoxide under mild conditions (equation 252).[501] This reaction presumably occurs outside the coordination

sphere of the metal, with the active species being alkoxy radicals resulting from the decomposition of the hydroperoxide by the metal, as previously shown for iron catalysts in equation (229).[502]



(252)

61.3.6.5 Copper Catalysts

61.3.6.5.1 Copper dioxygen complexes

The chemistry of copper superoxides, peroxides and oxo compounds is still poorly understood owing to the lack of structural data concerning these unstable species. Dioxygen is generally completely reduced by copper(I) salts. Reaction of copper(I) halides with O_2 in the presence of bases affords an active catalyst for the oxidative coupling of phenols; acetylenes and amines by O_2.[571,572] Complexes with the general formula $Cu_4X_4O_2L_n$ [$n = 3$ or 4; X = Cl, Br; L = py, MeCN, *N*-methylpyrrolidone (NMP), DMA, DMSO, *etc.*] have been isolated from the reaction of 4 mol copper(I) halide with 1 mol O_2 in the presence of a base.[572,575,582,583] Although no X-ray data are available as yet, it is generally understood that these tetrameric complexes involving two μ^2-oxo oxygen atoms are formed *via* homolytic dissociation of the μ-peroxo dioxygen adduct (**179**), followed by reaction of the $Cu^{III}{=}O$ or $Cu^{II}{-}O\cdot$ species (**180**) with the initial copper(I) complex (**178**).[14,572,573]

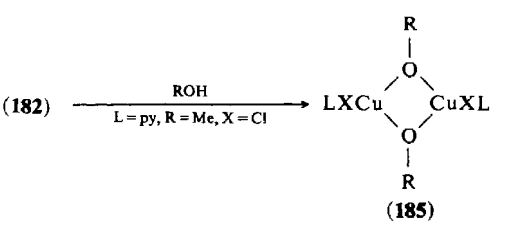
$$2LXCu^{I} + O_2 \rightarrow \underset{\textbf{(178)}}{LXCu^{III}{-}O{-}O{-}Cu^{II}XL} \rightarrow \underset{\textbf{(179)}}{2(LXCu^{III}{=}O \leftrightarrow LXCu^{II}{-}O\cdot)} \xrightarrow{LXCu^{I}} \underset{\textbf{(181)}}{LXCu^{II}{-}O{-}Cu^{II}XL} \qquad (253)$$

In the presence of trace amounts of water, the tetrameric μ^2-oxo complex (**182**) in 1,2-dimethoxyethane is transformed into a μ^4-oxo tetrameric complex (**183**; equation 254), characterized by an X-ray structure.[574] In contrast, (**182**)[572,575] is inactive towards the oxidation of phenols. The reaction of *N,N,N',N'*-tetramethyl-1,3-propanediamine (TMP) with CuCl, CO_2 and dioxygen results in the quantitative formation of the μ-carbonato complex (**184**; equation 255).[576] This compound acts as an initiator for the oxidative coupling of phenols by O_2.[576] Such μ-carbonato complexes, also prepared from the reaction of Cu(BPI)CO with O_2 [BPI = 1,3 bis(2-(4-methylpyridyl)imino)isoindoline],[577] are presumably involved as reactive intermediates in the oxidative carbonylation of methanol to dimethyl carbonate (see below).[578] Upon reaction with methanol, the tetrameric complex (**182**; L = Py; X = Cl) produces the bis(μ-methoxo) complex (**185**; equation 256), which has been characterized by an X-ray structure,[579] and is reactive for the oxidative cleavage of pyrocatechol to muconic acid derivatives.[580,581]

$$\underset{\textbf{(182)}}{(\mu_2\text{-}O)_2Cu_4X_4L_3} \xrightarrow[L = NMP]{H_2O} \underset{\textbf{(183)}}{(\mu^4\text{-}O)L_3Cu_4Cl_6(OH_2)L} \qquad (254)$$

$$CuCl \xrightarrow[L = TMP,\ X = Cl]{CO_2} LXCu{-}O{-}\underset{\underset{O}{\|}}{C}{-}O{-}CuXL \qquad (255)$$

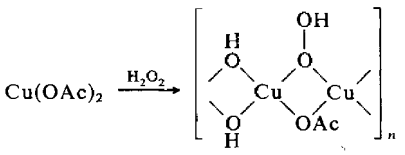
(184)



(256)

(185)

A polymeric μ-hydroperoxocopper(II) compound has been prepared from the reaction of hydrogen peroxide with an aqueous solution of copper(II) acetate and has been characterized by spectrophotometric methods and peroxide oxygen determination (equation 257).[222] Such copper(II) peroxide compounds have recently been claimed to be active catalysts for the epoxidation of light alkenes by dioxygen.[223]



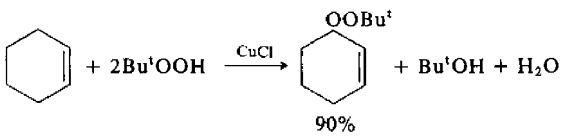
(257)

61.3.6.5.2 Oxidation of nonfunctionalized hydrocarbons

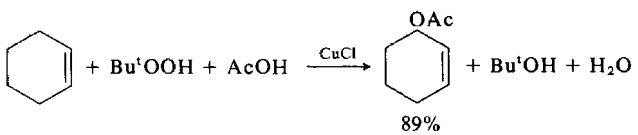
Catalytic oxidations by copper compounds are mainly homolytic in nature. Copper salts have been extensively used in conjunction with molecular oxygen, peroxides and persulfate for the oxidation of a variety of alkenic and aromatic hydrocarbons.[56,584]

(i) Oxidation of alkenes and alkynes

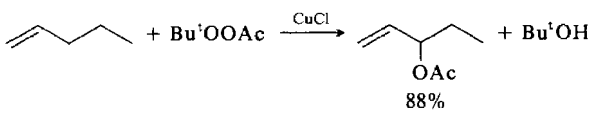
Copper(I) sulfate generated from the reduction of aqueous copper(II) sulfate with metallic copper promotes the epoxidation of alkenes such as allyl alcohol or propene in low yields.[585] The reaction of *t*-butyl hydroperoxide or *t*-butyl peracetate with alkenes in the presence of copper(I) chloride results in the homolytic formation of allylic *t*-butyl peroxides or allylic esters (equations 258–260).



(258)

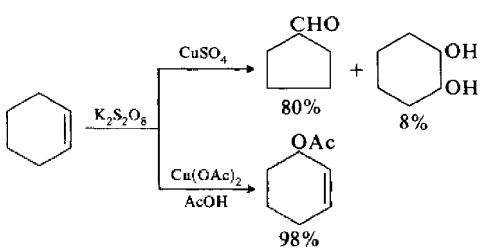


(259)



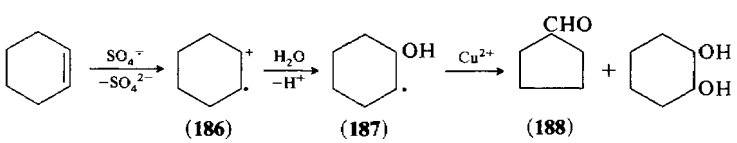
(260)

Oxidation of cyclohexene by peroxydisulfate in the presence of copper(II) salts results in the formation of cyclopentanecarboxaldehyde as the main product in an aqueous acetonitrile solution (equation 261), and 2-cyclohexenyl acetate in an acetic acid solution (equation 262).[588,589] Reaction (261) has been interpreted as the formation of a radical cation (**186**) by oxidation of cyclohexene with $S_2O_8^{2-}$, followed by hydrolysis of (**186**) to the β-hydroxyalkyl radical (**187**), which is oxidized by copper(II) salts to the rearranged aldehydic product (**188**; equation 263).[589]



(261)

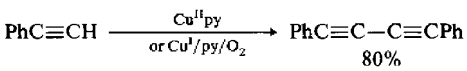
(262)



(263)

(186) (187) (188)

Monosubstituted acetylenic compounds can be oxidatively dimerized by air at room temperature in the presence of copper salts in a pyridine–methanol solution. This method has been applied to a wide variety of acetylenic compounds and gives high yields in disubstituted diacetylenic compounds (equation 264).[590]

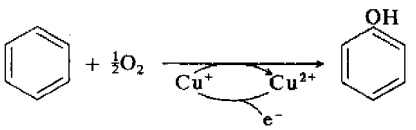


(264)

(ii) Oxidation of arenes

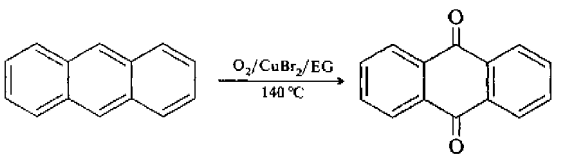
The reaction of hydrogen peroxide with copper(I) salts produces a Fenton-like hydroxylating system involving reactive hydroxyl radical intermediates (equation 265).[486,491] Hydroxylation of benzene to phenol can be achieved by air in the presence of copper(I) salts in an acidic aqueous solution.[592-593] This reaction is not catalytic (phenol yields are *ca.* 8% based on copper(I) salts) and stops when all copper(I) has been oxidized to copper(II). A catalytic transformation of benzene to phenol can occur when copper(II) is electrolytically reduced to copper(I) (equation 266).[594,595]

$$Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + OH^{-} + HO^{\cdot} \tag{265}$$



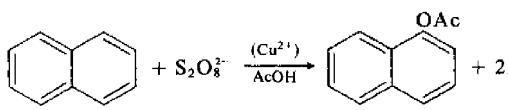
(266)

Anthracene can be selectively oxidized to anthraquinone by molecular oxygen in the presence of copper(II) bromide in an ethylene glycol solution. Ethylene glycol (EG) acts as a bidendate ligand for copper and prevents the formation of bromoanthracene as a by-product (equation 267).[596]

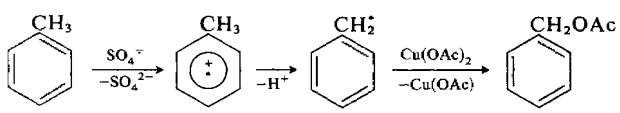


97% (267)

Nuclear[597] or side-chain[588,598] acetoxylation of arenes can be performed with good yields by persulfate and copper(II) salts in acetic acid (equations 268 and 269). As previously shown for cyclohexene (equation 263), persulfate oxidizes the aromatic ring to a radical cation which loses a proton to give a carbon radical, which is further oxidized by copper(II) acetate to the final acetoxylated product.



(268)



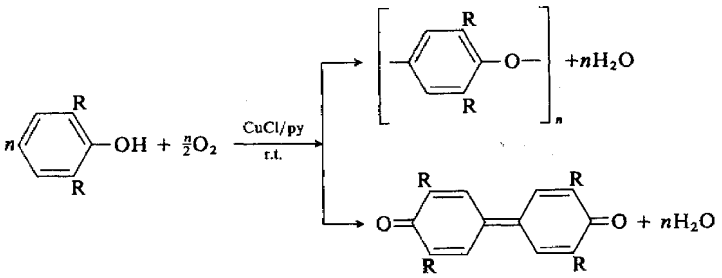
(269)

61.3.6.5.3 Oxidation of phenols

Copper-catalyzed oxidations of phenols by dioxygen have attracted considerable interest owing to their relevance to enzymic tyrosinases (which transform phenols into *o*-quinones; equation 24) and laccases (which dimerize or polymerize diphenols),[67] and owing to their importance for the synthesis of specialty polymers [poly(phenylene oxides)][599] and fine chemicals (*p*-benzoquinones, muconic acid). A wide variety of oxidative transformations of phenols can be accomplished in the presence of copper complexes, depending on the reaction conditions, the phenol substituents and the copper catalyst.[56]

(i) Oxidation of monophenols

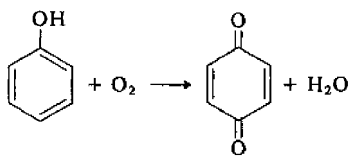
Copper(I) salts in the presence of a tertiary amine catalyze the oxidation of 2,6-disubstituted phenols by O_2 into poly(phenylene oxides) (high amine/copper ratio) or biphenyl-4,4′-quinones (low amine/copper ratio). When R is a bulky substituent (*e.g.* Bu^t), biphenyl-4,4′-quinone is the sole product (equations 270 and 271).[599]



(270)

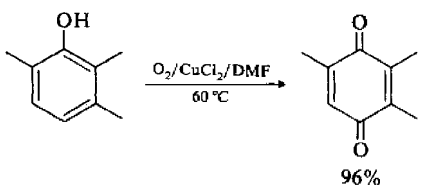
(271)

Under different reaction conditions, phenols can be oxidized to *p*-quinones (equations 272[600–602] and 273[603]), but in the case of phenol itself, insufficient selectivity has prevented, as yet, the commercial application of this potentially important synthesis of *p*-benzoquinone and hydroquinone. The selectivity of *p*-benzoquinone, or *p*-quinol formation can be increased at the expense of oxidative coupling products by using a large excess of the copper reagent [$Cu_4Cl_4O_2(MeCN)_3$ or $CuCl+O_2$ in MeCN] with respect to the phenolic substrate.[604] The suggested mechanism involves the oxidation of the phenoxide radical (**189**) by a copper(II)-hydroxo species to *p*-quinol (**190**) which can rearrange (for $R^2=H$) to hydroquinone (**191**; Scheme 14), which is readily oxidizable to *p*-quinone.[604]

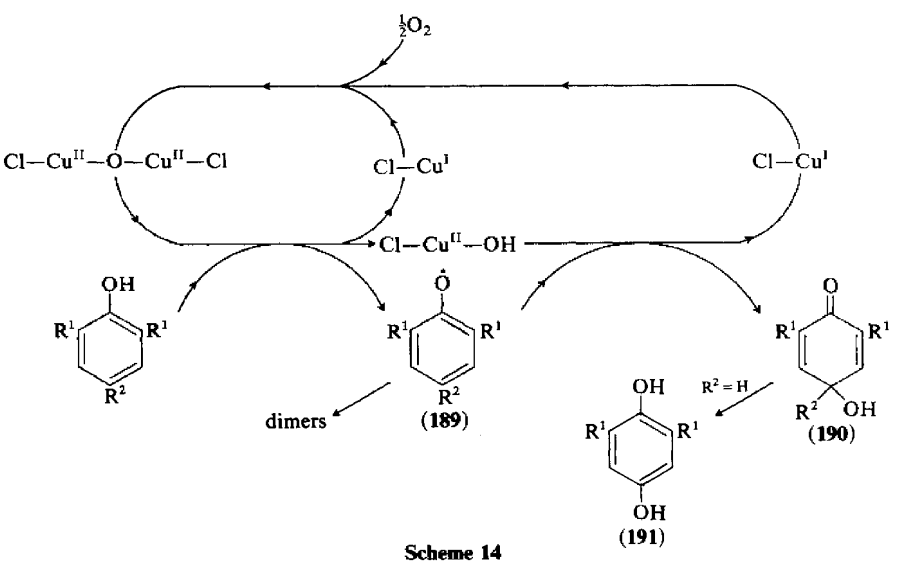


(272)

$CuCl/MeCN/O_2$(70 bar)[600] C = 93%, S = 80%
$CuCl/MeOH/O_2$(100 bar)[602] C = 89%, S = 60%

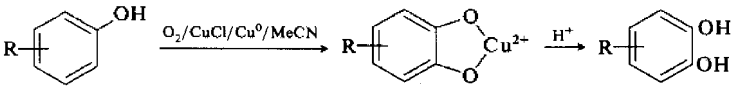


(273)



Scheme 14

Ortho hydroxylation of phenols can be accomplished by molecular oxygen in the presence of copper(I) chloride and metallic copper in acetonitrile. This particular *ortho* selectivity, which is similar to that of enzymic tyrosinases, has been attributed to the formation of a stable copper(II) catecholate resulting from the reaction of copper(I) phenates with dioxygen (equation 274).[605]



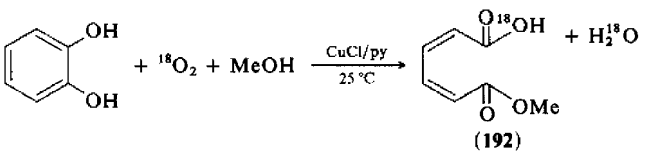
70–90% (274)

(ii) Oxidative cleavage of catechols

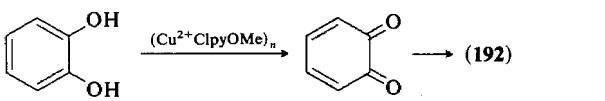
Tsuji and coworkers reported that copper(I) chloride in the presence of pyridine, methanol and dioxygen promotes the stoichiometric oxidation of pyrocatechol to methyl muconate.[606] Labeling $^{18}O_2$ studies have shown that only one atom of the dioxygen molecule is incorporated in the substrate, while the other one is transformed into water as in enzymic monooxygenases (equation 275)[607] (and not as in dioxygenases, *viz.* pyrocatechase). This reaction has been shown by Rogic *et al.* to proceed *via* two steps (equation 276).[580,581]

(a) The first step is the oxidation of pyrocatechol to *o*-quinone by the 'cupric reagent', which has the presumed formula $[Cu^{II}Cl(OMe)py]_n$ related to complex (**185**; equation 256).[579] This reaction presumably involves formation of a dicopper(II) catecholate intermediate in which electron transfer from the aromatic ring to two Cu^{II} centers provides *o*-benzoquinone and two copper(I) species, reoxidized by O_2 to copper(II).[581]

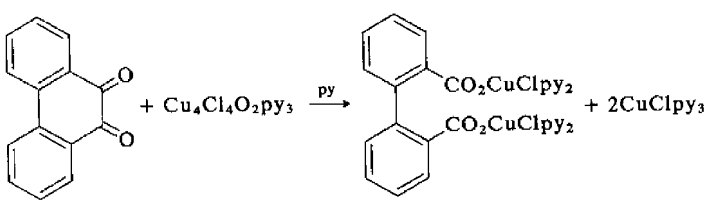
(b) The second step is the oxidative cleavage of the *o*-benzoquinone to methyl muconate induced by the 'cupric reagent'.[581] Such an oxidative cleavage reaction of 9,10-phenanthrenequinone by $Cu_4Cl_4py_3O_2$ (**182**) has been shown to occur stoichiometrically in argon (equation 277).[582]



(**192**) (275)



(276)



(277)

61.3.6.5.4 Oxidation of alcohols

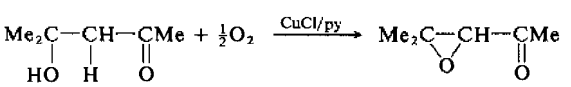
Copper(I) chloride in the presence of pyridine derivatives catalyzes the oxidation of alcohols to the corresponding carbonyl compounds by molecular oxygen.[608] The best catalytic system involves 1,10-phenanthroline as the basic ligand and is well suited for the oxidation of benzylic or allylic alcohols (equation 278 and 279). Cycloalkanols are poorly reactive, and linear primary alcohols give a large amount of aldehydic oxidation products having at least one less carbon atom than the initial substrate. Diacetone alcohol can be oxidatively dehydrogenated to the corresponding α-keto epoxide by dioxygen in the presence of CuCl and pyridine (equation 280).[609]

$$PhCH_2OH + \tfrac{1}{2}O_2 \xrightarrow{CuCl/phen} PhCHO + H_2O \quad (278)$$

86%

$$PhCH{=}CHCH_2OH + \tfrac{1}{2}O_2 \xrightarrow{CuCl/phen} PhCH{=}CHCHO + H_2O \quad (279)$$

83%



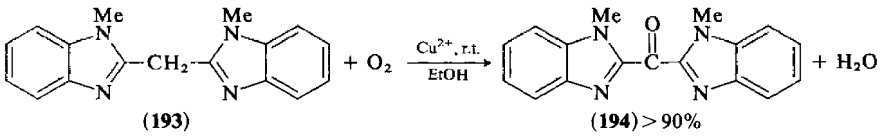
(280)

C = 28%, S = 95%

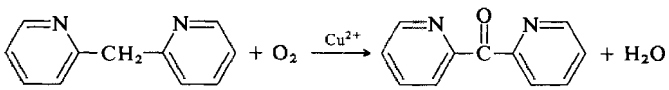
61.3.6.5.5 Oxidation of nitrogen compounds

(i) Oxidation of methylene to carbonyl groups

Copper salts catalyze the selective transformation of activated methylene groups into carbonyl groups by dioxygen. These reactions (281)–(283) can be considered as valid models for enzymic internal monooxygenases (equation 22), since ^{18}O labeling studies have shown that the carbonyl oxygen atom of (**194**) comes from molecular oxygen.[610] Oxidation of bis(1-methylbenzimidazol-2-yl)methane (**193**; equation 281)[610] and bis(2-pyridyl)methane (**195**; equation 282)[611] results in the formation of the carbonyl compounds (**194**) and (**196**), respectively, in almost quantitative yields. Copper(II) salts also catalyze the selective transformation of trimethylamine into dimethylformamide (equation 283).[612]



(193) (194) > 90% (281)



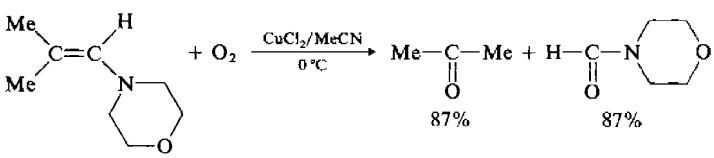
(195) (196) > 90% (282)

$$Me_2NMe + O_2 \xrightarrow[110\,^\circ C]{CuCl_2/DMF} Me_2N{-}\overset{\overset{O}{\|}}{C}{-}H + H_2O \quad (283)$$

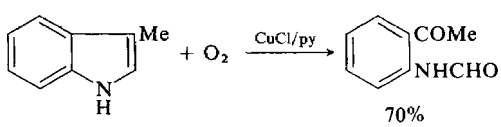
C = 40%, S = 99%

(ii) Oxidative cleavage of activated double bonds

Copper complexes are particularly effective catalysts for the oxidative cleavage of enamines (equation 284)[613,615] and 3-substituted indoles (equation 285)[616,617] under extremely mild conditions (~0 °C).



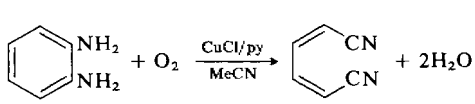
87% 87% (284)



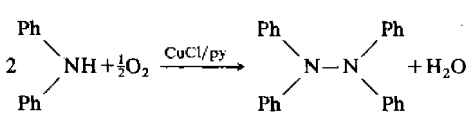
70% (285)

(iii) Miscellaneous oxidations

Several specific oxidative transformations of nitrogen compounds can be carried out in the presence of copper salts. Oxidation of *o*-phenylenediamine with molecular oxygen in the presence of a twofold excess of CuCl in pyridine results in the formation of *cis,cis*-muconitrile in high yield (equation 286).[618-619] The bis-μ-oxo tetranuclear complex $Cu_4Cl_4O_2(py)_4$ was found to be the active species in this transformation.[618] A similar procedure can be used for the selective oxidative coupling of diphenylamine to tetraphenylhydrazine by $CuCl/py/O_2$ or $Cu_4Cl_4O_2py_4$ (equation 287).[619]



96% (286)



83% (287)

Copper(II) acetate in methanol catalyzes the oxidation in air of acid hydrazides to carboxylic acids or esters (equation 288),[621] and that of 1,2-dihydrazones to acetylenes (equation 289).[618]

$$\mathrm{Ph{-}\overset{\overset{\mathrm{O}}{\|}}{C}{-}NHNH_2 + O_2 \xrightarrow{Cu(OAc)_2/MeOH} PhCO_2H + N_2 + H_2O} \quad (288)$$

95%

$$\mathrm{PhC(=NNH_2){-}CPh(=NNH_2) + O_2 \xrightarrow{Cu(OAc)_2/MeOH} PhC{\equiv}CPh + 2N_2 + 2H_2O} \quad (289)$$

78%

61.3.6.5.6 Oxycarbonylation of alcohols and amines

It has long been known that copper(I) salts in complexing solvents absorb carbon monoxide under mild conditions,[621] and several copper(I)-carbonyl complexes having terminal CO (*e.g.* $[Cu(dien)CO]BPh_4$, dien = diethylenetriamine[522]; $CuHB(C_3N_2H_3)CO$, $HB(C_3N_2H_3)_3$ = hydrotris(1-pyrazolyl)borato[623]) or bridging CO (*e.g.* $[Cu_2(tmen)_2(\mu\ CO)(\mu\ PhCO_2)]BPh_4$[624]) have been characterized by an X-ray crystal structure. As previously shown in equation (255), μ-carbonato-copper(II) complexes can be generated from the reaction of copper(II)-μ-oxo complexes with CO_2, or from the reaction of copper(I) CO complexes with O_2. These μ-carbonato complexes are probably the precursors for the synthesis of dimethyl carbonate by oxycarboxylation of methanol.

Dimethyl carbonate is an interesting material which can be used instead of toxic dimethyl sulfate as a multipurpose alkylating reagent.[438,578] Its synthesis can be performed in one step from cheap methanol, CO and oxygen materials in the presence of copper salts (*e.g.* copper(II) methoxychloride or CuCl/py) at *ca.* 100 °C and 15–70 atm (equation 290).[578,625] This reaction is thought to proceed in two steps:[578] (a) formation of copper(II) methoxychloride from the reaction of copper(I) chloride, O_2 and methanol (equation 291) and (b) reduction of copper(II) methoxychloride with CO to form dimethyl carbonate and regenerate copper(I) chloride (equation 292).[626]

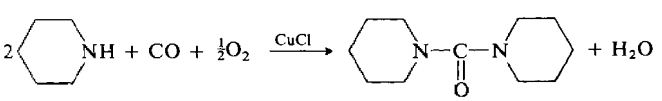
$$\mathrm{2MeOH + CO + \tfrac{1}{2}O_2 \xrightarrow{CuClOMe} MeO{-}\overset{\overset{\mathrm{O}}{\|}}{C}{-}OMe + H_2O} \quad (290)$$

C ≈ 10–20%, S > 90%

$$2CuCl + 2MeOH + \tfrac{1}{2}O_2 \rightarrow 2CuClOMe + H_2O \quad (291)$$

$$2CuClOMe + CO \rightarrow (MeO)_2C{=}O + 2CuCl \quad (292)$$

A related oxycarbonylation of secondary amines to *N,N*-disubstituted ureas in the presence of copper(I) salts at room temperature and atmospheric pressure has been disclosed by Brackman.[626a] The reaction is particularly effective with cyclic secondary amines such as piperidine and morpholine (equation 293), with primary and aliphatic secondary amines being much less reactive.[626a]



(293)

61.3.7 CONCLUDING REMARKS

In general, the catalytic properties of transition metals for the oxidation of hydrocarbons are strongly governed by the existence and nature of the metal-oxygen intermediates. Among the various possible reactive intermediates, two families of metal-oxygen species emerge as the most important ones, *i.e.* metal peroxides and metal-oxo compounds.

In metal peroxide chemistry, the heterolytic or homolytic nature of catalytic oxidation seems to be strongly dependent on the heterolytic or homolytic dissociation mode of the peroxide intermediate, for which the triangular coordination mode of the peroxide moiety of the metal appears to be a key feature. Heterolytic oxidations require attainable coordination sites on the metal, involve strained metallacyclic reaction intermediates, and are highly selective. In contrast, homolytic oxidations involve bimolecular radical processes with no metal-substrate interactions and are less selective. In the important field of palladium oxidation chemistry, hydroperoxo

species probably play an important role in the reoxidation of palladium hydride by air, which is a key step for achieving the catalytic oxidation cycle.

Although stoichiometric oxidations by high-valent d^0 oxo compounds have been firmly established, a recent approach using first-row transition metal porphyrins and various oxidants (O_2+ coreductant, peroxides, PhIO, NaOCl) has raised the possibility that high-valent metal-oxo species (*e.g.* $Cr^V{=}O$, $Mn^V{=}O$, $Fe^V{=}O$) could act as the key intermediate oxidants for the epoxidation of alkenes and the hydroxylation of alkanes. Although these oxidations are homolytic in nature, they can be controlled for better stereoselectivity and enantioselectivity by changing the substituents on the porphyrin periphery. The oxidizing properties of iron- and cobalt-μ^3-oxo species $M_3O(RCO_2)_6L_3$ and of copper(II)-μ^3-oxo complexes $Cu_4X_4O_2L_3$ also seem to be of particular interest and can be considered as possible precursors for reactive first-row metal-oxo species.

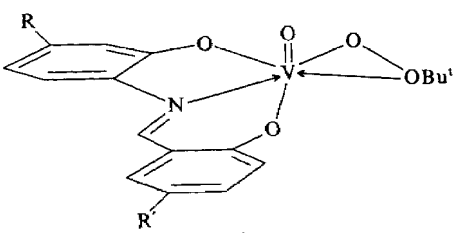
Except for a few cases (*e.g.* the rhodium-catalyzed ketonization of terminal alkenes), the direct and selective oxidation of hydrocarbons by molecular oxygen without the need for a coreducing agent has proved to be difficult to achieve owing to the different reactivities of the first peroxide oxygen atom and of the second oxo or hydroxo oxygen atom of the coordinated dioxygen molecule. New approaches using metal-oxo oxidants which can be regenerated by air, or nitro-metal complexes, are interesting alternatives which deserve to be pursued. Intensive efforts by many groups of researchers, including organic and inorganic chemists and biochemists, in the area of oxidation chemistry should ensure that this goal will probably be achieved in the near future so as to provide a larger number of well-characterized oxidizing reagents and new selective catalytic transformations.

61.3.8 ADDENDUM

Since this chapter was written, several review articles,[627,627a,628] and a number of significant new papers have appeared. They are briefly noted here in relation to the most relevant sections of the text.

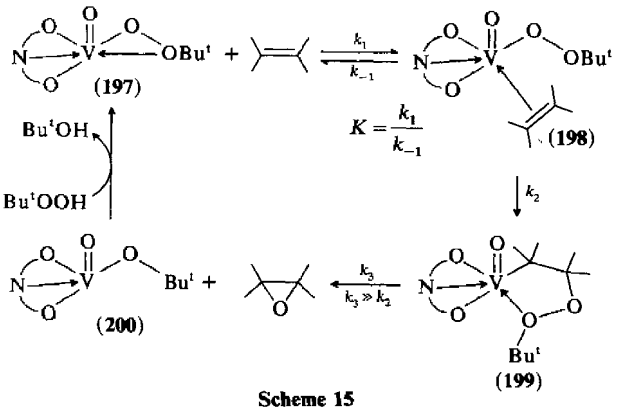
Section 61.3.2 Metal Peroxides in Oxidation

Novel vanadium(V)-alkyl peroxide complexes with the general formula $VO(OOBu^t)(ROPhsalR')$ (**197**; ROPhsalR′ = tridendate *N*-(2-oxidophenyl)salicylidenaminato Schiff base ligand) were found to epoxidize alkenes stoichiometrically with high selectivity.[629]



(**197**)

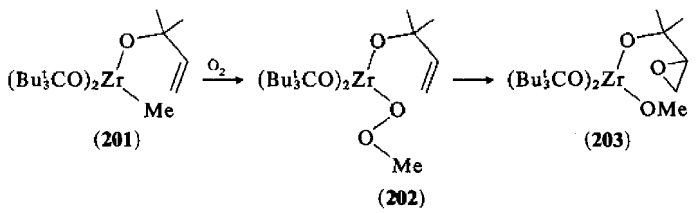
The reactivity of complexes (**197**) is highly relevant to the Halcon epoxidation process (see Section 61.3.2.2.1). The reaction proceeds at room temperature with high yields, and is completely stereoselective (*cis*-alkenes are transformed into *cis*-epoxides only). The reactivity of alkenes increases with their nucleophilic nature, as for MoO_5(HMPA) complexes. The reaction is strongly inhibited by water, alcohols and basic ligands, and is accelerated in polar nondonor solvents ($C_2H_4Cl_2$, $PhNO_2$). The Michaelis-Menten epoxidation rate $V = k_2K[\text{alkene}][\text{complex}]/(1 + K[\text{alkene}])$ shows that the alkene reversibly coordinates to the metal, forming a metal-alkene adduct which decomposes in the rate determining step to the epoxide and the metal *t*-butoxy complex. The proposed mechanism (Scheme 15) involves the coordination of the alkene to vanadium(V), displacing the weakly bonded OBu^t oxygen atom, followed by the insertion of the coordinated alkene into the V—O bond, forming the pseudocyclic metalladioxetane (**199**) which decomposes by a [1,3] dipolar cycloreversion mechanism to the epoxide and the vanadium(V)-*t*-butoxy complex (**200**). The reaction becomes catalytic in the presence of excess Bu^tOOH.[629]



Scheme 15

The heterolytic reactivity of complex (**197**) contrasts with the homolytic reactivity of the vanadium(V) (dipicolinato)(alkyl peroxide) (**22**), and is presumably due to the lower binding ability of the OBu^t oxygen atom in (**197**), shown by NMR, which allows the coordination of alkene to the metal.

In the Halcon epoxidation process, the reaction of the zirconium(IV) methyl trialkoxide (**201**) with O_2 yields the epoxy alkoxide (**203**), *via* intramolecular epoxidation of the coordinated allyl alcohol by the incipient methyl peroxide complex (**202**).[630]

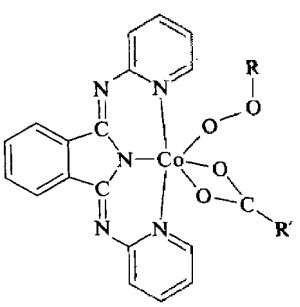


(294)

t-Butylperoxy complexes of bis(pentamethylcyclopentadienyl)hafnium(IV) [$(C_5Me_5)_2Hf(OOBu^t)R$; **204**; R = Me, Et, Ph] have been prepared from the reaction of Bu^tOOH with $(C_5Me_5)Hf(H)(R)$, and thermally decompose to give the mixed alkoxide $(C_5Me_5)Hf(OBu^t)(OR)$. The X-ray crystal structure of (**204**; R = Ph) indicates a monodendate *t*-butylperoxy ligand.[631]

Titanium(IV)-porphyrin [TiO(TPP)] as well as molybdenum(V)-porphyrin [MoO(OMe)(TPP)] complexes were found to be active for the catalytic epoxidation of alkenes by alkyl hydroperoxides, whereas their peroxo derivatives are inactive.[632] Iron(III)-porphyrin-peroxo complexes such as $Fe(TPP)O_2^-NMe_4^+$ did not react with hydrocarbons, but form sulfato complexes upon reaction with SO_2.[632] Manganese(III)-porphyrin-peroxo complexes $Mn(O_2)(TPP)^-K^+$ were recently characterized by X-ray crystallography.[634]

Cobalt(III)-alkyl peroxide complexes with the formula Co(BPI)(OOR)(OCOR') (**205**; BPI = 1,3-bis(2'-pyridylimino)isoindoline; R = Bu^t, CMe_2Ph; R' = Me, Ph, Bu^t) have been prepared from the oxidation of $Co^{II}(BPI)(OCOR')$ complexes by alkyl hydroperoxides. The X-ray crystal structure of complex (**205**); (R = Bu^t, R' = Ph) revealed a distorted octahedral environment, with a monodendate $OOBu^t$ group and a bidendate carboxylate.[635]



(**205**)

Saturated hydrocarbons are homolytically oxidized by complexes (**205**) into alcohols, ketones and *t*-butyl peroxide products. The hydroxylation reaction occurs at the more nucleophilic C—H

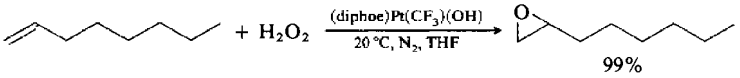
bonds, with extensive epimerization at the hydroxylated carbon atoms. The following mechanism has been suggested (equation 295).

$$LnCo^{III}—OOBu^t \xrightarrow{-Bu^tO\cdot} LnCo^{III}—O\cdot \xrightarrow{RH} LnCo^{III}—OH + R\cdot \rightarrow LnCo^{II} + ROH \quad (295)$$

Ln = (BPI)(OCOR)

These complexes (**205**) were found to be good models for the reactive intermediates involved in the catalytic decomposition of alkyl hydroperoxides (Haber Weiss mechanism), and in the catalytic hydroxylation of hydrocarbons by ROOH.

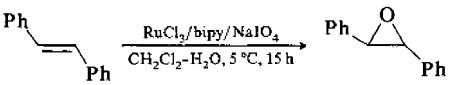
The platinum complex (diphoe)Pt(CF_3)(OH) is an effective catalyst for the selective epoxidation of terminal alkenes by dilute H_2O_2 under mild conditions (20 °C). The reaction is thought to proceed *via* external attack of the HOO^- anion on the coordinated alkene (equation 296).[636]



99% (296)

Section 61.3.3 Metal–Oxo Complexes in Oxidation

In the presence of excess bipyridyl, ruthenium trichloride is an effective catalyst for the selective epoxidation of alkenes by sodium periodate (equation 297). The epoxidation is *syn* and stereospecific for *cis* and *trans* alkenes.[637]



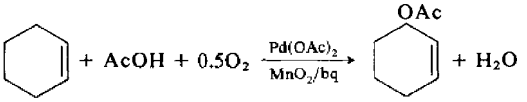
83% (297)

Ruthenium-oxo species $(RuO_4)^{2-}$ and $(RuO_4)^-$ oxidize primary alcohols to carboxylic acids and secondary alcohols to ketones. New species $(RuO_2Cl_3)(PPh_4)$ and $RuO_2(bipy)Cl_2$ cleanly oxidize a wide range of alcohols to aldehydes and ketones without attack of double bonds.[638]

Section 61.3.4 Palladium-catalyzed Oxidations

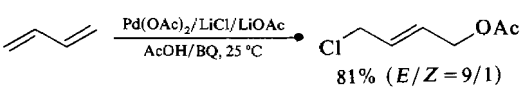
The synthetic applications of the palladium-catalyzed oxidation of alkenes to ketones have recently been reviewed.[639] Improvements in the Wacker palladium-catalyzed ketonization of terminal alkenes have been obtained using phase-transfer catalysis,[641] polyethylene glycol[642] or phosphomolybdovanadic acids.[643]

Allylic acetoxylation of cyclohexene can be selectively effected by palladium acetate in the presence of MnO_2 and *p*-benzoquinone (bq) (equation 298).[640]



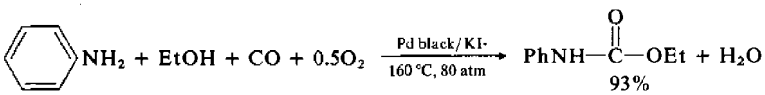
95% (298)

Palladium-catalyzed oxidation of 1,3-dienes in the presence of LiCl and LiOAc produces 1-acetoxy-4-chloro-2-alkenes with high selectivity. The reaction is stereospecific and cyclic dienes give an overall *cis* [1,4] addition (equation 299).[644]



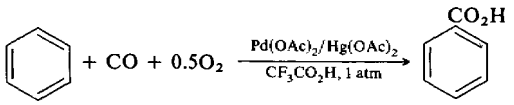
81% (*E*/*Z* = 9/1) (299)

Carbamates have been prepared in good yields from the reaction of amines, alcohols, CO and oxygen in the presence of palladium or rhodium catalysts and iodide (equation 300).[645]



93% (300)

The oxidative carbonylation of aromatic hydrocarbons can be effected under mild conditions (r.t., 1 atm CO) in CF_3CO_2H in the presence of an equimolecular mixture of $Pd(OAc)_2$ and $Hg(OAc)_2$ (equation 301).[646]



(301)

Section 61.3.5 Oxidation by Coordinated Nitro Ligands

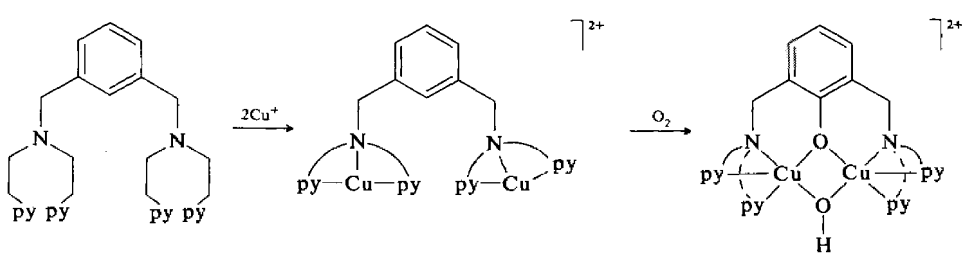
This subject has recently been reviewed.[647] Several additional papers have appeared on the catalytic oxidation of alkenes by O_2 in the presence of $PdCl(MeCN)_2NO_2$(**148**).[648] Terminal alkenes and *trans*-cyclooctene yield the corresponding ketones, cyclopentene and cyclohexene the corresponding allyl alcohol, and bicyclic alkenes the corresponding epoxide. Heterometallacyclopentanes such as (**152**) have been isolated from the reaction of (**148**) with norbornene (dicyclopentadiene), and characterized by X-ray crystallography.[648d] Glycol monoacetates were obtained from the reaction of (**148**) with terminal alkenes in acetic acid.[649]

Section 61.3.6 Catalysis by First-row Transition Metal Complexes (Mn, Fe, Co, Cu)

The epoxidation of alkenes by sodium hypochlorite in the presence of manganese porphyrins under phase-transfer conditions has been thoroughly studied.[650,651] Kinetic studies of this reaction revealed a Michaelis–Menten rate equation.[652] As in Scheme 12, the active oxidant is thought to be a high-valent manganese(V)–oxo–porphyrin complex which reversibly interacts with the alkene to form a metal oxo–alkene intermediate which decomposes in the rate determining step to the epoxide and the reduced Mn^{III} porphyrin. Shape selective epoxidation is achieved when the sterically hindered complex Mn(TMP)Cl is used as the catalyst in the hypochlorite oxidation.[652] Other oxygen sources, such as potassium hydrogen sulfate,[653] ROOH,[654] O_2+ascorbate[655] or $NaBH_4$,[656] and iodosylbenzene,[657] have also been used in conjunction with manganese porphyrins for the epoxidation of alkenes and the hydroxylation of alkanes. In the presence of imidazole, manganese porphyrins catalyze the epoxidation of alkenes, including the terminal ones, by hydrogen peroxide.[658] Nonene epoxide was obtained in 90% yield using 5 equivalents of H_2O_2 at 20 °C in MeCN in the presence of catalytic amounts of Mn(TDCPP)Cl and imidazole (TDCPP = tetra-2,6-dichlorophenylporphyrin).[658] The catalyst was not destroyed at the end of the reaction.

In relation to enzymic cytochrome *P*-450 oxidations, catalysis by iron porphyrins has inspired many recent studies.[659–663] The use of C_6F_5IO as oxidant and Fe(TDCPP)Cl as catalyst has resulted in a major improvement in both the yields and the turnover numbers of the epoxidation of alkenes.[659] The Michaelis–Menten kinetic rate, the higher reactivity of alkyl-substituted alkenes compared to that of aryl-substituted alkenes, and the strong inhibition by norbornene in competitive epoxidations suggested that the mechanism shown in Scheme 13 is heterolytic and presumably involves the reversible formation of a four-membered Fe^V–oxametallacyclobutane intermediate.[660] Picket-fence porphyrin (TPiVPP)FeCl–imidazole, O_2 and [H_2+colloidal Pt supported on poly(vinylpyrrolidone)] act as an artificial *P*-450 system in the epoxidation of alkenes.[663]

Cu^{2+} ions, *e.g.* $Cu(NO_3)_2$, catalyze the epoxication of alkenes by iodosylbenzene.[664] Oxidation of alcohols to aldehydes can be effected by O_2 in the presence of Cu^{2+} ions and Tempo (2,2,6,6-tetramethylpiperidinyl 1-oxide).[665] Arene hydroxylation of the binucleating ligand (**206**)



(302)

(**206**) (**207**) (**208**)

by O_2 is catalyzed by copper(I) salts, presumably *via* the intermediate formation of a μ-peroxo $Cu^{II}—OO—Cu^{II}$ species. Complex (**208**) has been characterized by means of an X-ray crystal structure.[666]

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61.4

Lewis Acid Catalysis and the Reactions of Coordinated Ligands

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61.4.1 INTRODUCTION

Metal ions are Lewis acids and as such catalyze many reactions which are also subject to specific acid catalysis by the proton. Reactions in which metal ions are involved are often best described as metal ion-promoted reactions as the products of the reaction often remain bound to the metal ion. Although scattered references to metal ion-promoted reactions are to be found in the early literature it was not until the late 1950s that such reactions began to be studied in detail. A strong driving force has been the realization that some 30% of enzymes are metalloenzymes or require metal ions for activity. Many of the reactions dealt with in this article have been studied in an attempt to delineate possible mechanisms for enzymic processes.

Before considering the consequences of the coordination of substrates to metal centres, it is instructive to compare some of the properties of metal ions with those of the proton.

(1) The proton, although limited to a single positive charge, has an extremely high charge density and therefore great polarizing power. The charge density on a metal ion due to its larger size is generally much less. The charge density on Pt^{IV} may approach that of H^+ and its effect can be seen in the properties of complexes of this metal ion (*e.g.* pK_a values and reactivity of coordinated amines and water).[1]

(2) The coordination number of the proton is usually one, although it can be greater if hydrogen bonding is considered. The larger coordination numbers of the transition metal ions allow them more flexibility in grouping reagents for intramolecular reactions.

(3) The concentration of protons (and of protonated substrates) is limited at pH values near neutrality. Analogous metal complexes are often stable over a wide pH range including physiological pH, and may exist in the presence of appreciable concentrations of OH^- or other nucleophiles. Westheimer[2] coined the term 'superacid catalysis' to describe the ability of metal ions to catalyze reactions at pH values where substantial concentrations of the protonated substrates cannot exist.

If a substrate is subject to specific acid catalysis by a proton then it is likely that an analogous Lewis acid-catalyzed reaction will occur. If the substrate becomes less reactive on protonation, then similar effects will be observed with the metal ion complex. The activating or protective effect of coordination arises from withdrawal of electron density from the ligand by the metal ion. In complexes where there is substantial π-character in the metal–ligand bond, back donation of electron density from filled *d*-orbitals on the metal ion into, for example, π^*-antibonding ligand orbitals may result in little or no net electron withdrawal, or in some cases a net gain.[1] In these systems the effect of coordination on the reactivity of the ligand will be minimal.[3]

Table 1 Rate Constants for the Bromination of Aniline, the Anilinium Ion and a Metal Complex[a]

Substrate	$k(M^{-1}\,s^{-1})$
$PhNH_2$	3×10^{10}
cis-$[Co(en)_2Cl(NH_2Ph)]$	1.4×10^{-1}
$PhNH_3^+$	3×10^{-7}

[a] Data taken from M. M. Jones, 'Ligand Reactivity and Catalysis', Academic, New York, 1968.

The Lewis acidity of a particular metal ion will be primarily a function of the charge density on the metal centre. Complexes of Cu^{II}, Zn^{II} and Co^{III} should therefore display properties intermediate between those of the free ligand and its conjugate acid. Early measurements on the bromination of aniline, the anilinium ion and coordinated aniline provide a good illustration of this point (Table 1). Since this reaction is an electrophilic substitution, protonation and metal

complex formation inhibit the reaction. Many of the examples to be discussed in the chapter deal with accelerated rates of nucleophilic attack due to the coordination of a carbonyl group *via* a one pair on oxygen, or a nitrile group through its nitrogen atom which leads to an increased susceptibility of the carbon atom to nucleophilic attack. Although the metal complex is less reactive than the protonated substrate, it can exist at pH values where the concentration of the protonated substrate can be negligible. For this reason many hydrolytic enzymes have metals such as $zinc^{II}$ at the active site. Enzymes use general acid catalysis and metal ion catalysis rather than the specific acid catalysis normally employed by the synthetic chemist.

Several books and review articles are available dealing with various aspects of metal ion catalysis,[4-24,29-32] and the role of metal ions in enzymic catalysis.[25-28]

61.4.1.1 The Hydrolysis of Cations

Metal ions in aqueous solution generally hydrolyze to form a series of mononuclear and polynuclear hydroxy complexes.[33,34] Iron(III) for example forms $[FeOH]^{2+}$, $[Fe(OH)_2]^{+}$, $Fe(OH)_3(aq)$, $[Fe(OH)_4]^{-}$, $[Fe_2(OH)_2]^{4+}$ and probably other polynuclear species. The formation of a monohydroxy complex (equation 1) can be used as a guide to the degree of electron withdrawal by the cation. Typical pK_a values for various cations are listed in Table 2. (The pK_a values of H_3O^+ and H_2O are -1.7 and 15.7 respectively.) The tetrahedrally coordinated $[Be(H_2O)_4]^{2+}$ ion is more acidic than expected when compared with octahedrally coordinated aqua ions of divalent metals. Each hydrogen must carry a somewhat greater portion of the positive charge than it would in an octahedral complex, and this makes removal of a proton easier. Similar considerations apply to square planar $Pd^{2+}(aq)$. Mercury(II) and tin(II) are also more acidic than would be expected. The high acidity of mercury(II) is due to the unusual stability of 'linear' $H_2O{-}Hg{-}OH^+$, while $Sn^{II}(aq)$ has between two and three coordinated water molecules in the inner coordination sphere.[35]

$$M^{n+}{-}O\begin{matrix}H\\ \diagup\\ \diagdown\\ H\end{matrix} \overset{K_a}{\rightleftharpoons} M{-}OH^{(n-1)+} + H^+ \qquad (1)$$

Table 2 The pK_a Values of Aqua Cations[a]

Ion	pK_a	*Ion*	pK_a
Al^{III}	4.97	Pd^{II}	−2.3
Be^{II}	5.40	Pb^{II}	7.71
Bi^{III}	4.0	Mn^{II}	10.59
Cd^{II}	10.08	Ni^{II}	9.86
Co^{II}	9.65	Pu^{IV}	0.5
Cu^{II}	7.96	Tl^{III}	0.62
Er^{III}	7.9	Th^{IV}	3.2
Hf^{IV}	0.25	U^{IV}	0.65
Fe^{III}	2.19	Zn^{II}	8.96
		Zr^{IV}	−0.3

[a] Data from D. W. Barnum, *Inorg. Chem.* 1983, **22**, 2297.

61.4.1.2 The Kinetic Investigation of Metal-promoted Reactions Involving Labile Metal Ions

Most metal ion-promoted reactions in which labile metal ions are employed involve a reaction scheme of the type shown in equations (2)–(5). There is a rapid pre-equilibrium formation of MS^{2+} (M^{2+} = metal ion; S = substrate) (equation 2), which can be followed by attack of hydroxide ion (equation 3) of water (equation 4) to give products. In some cases unimolecular decomposition of MS^{2+} occurs, as for example in decarboxylation reactions (Section 61.4.6). Most reactions are studied with a constant substrate concentration and a varying excess of the metal ion under constant conditions of pH. Plots of k_{obs} (the observed first order rate constant) *versus* the metal ion concentration can be of two types (Figures 1 and 2). In Figure 1, there is a linear dependence on the $[M^{2+}]$, indicating limited complex formation. The slope of the line $k_{obs}/[M^{2+}]$ gives the catalytic rate constant k_{cat}. The behavior shown in Figure 2 illustrates 'saturation' conditions. At high metal ion concentrations the reaction rate becomes independent of the metal ion concentration due to complete formation of the complex MS^{2+}. Such plots can be used to obtain both rate

constants and equilibrium constants. In this case it can readily be shown that k_{obs} is given by equation (6) which can be rearranged to give equation (7).

$$M^{2+} + S \underset{}{\overset{K}{\rightleftharpoons}} MS^{2+} \quad (2)$$

$$MS^{2+} + OH^- \xrightarrow{k_{OH}} \text{products} \quad (3)$$

$$MS^{2+} + H_2O \xrightarrow{k_{H_2O}} \text{products} \quad (4)$$

$$MS^{2+} \xrightarrow{k} \text{products} \quad (5)$$

$$k_{obs} = \frac{kK[M^{2+}]}{1 + K[M^{2+}]} \quad (6)$$

$$\frac{1}{k_{obs}} = \frac{1}{kK[M^{2+}]} + \frac{1}{k} \quad (7)$$

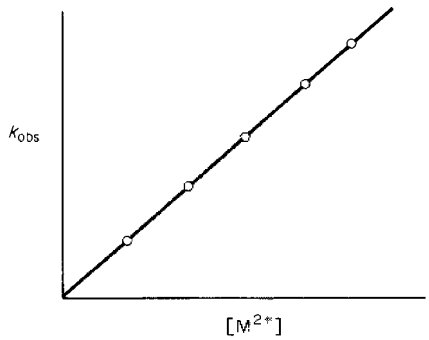


Figure 1

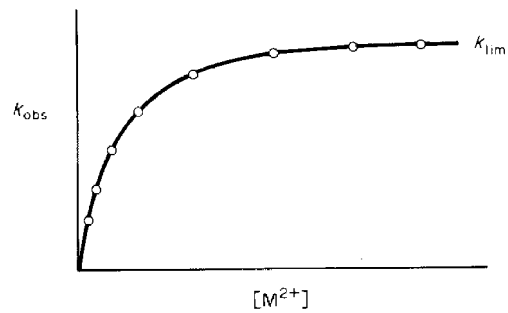


Figure 2

A plot of $1/k_{obs}$ *versus* $1/[M^{2+}]$ is linear of slope $1/kK$ and intercept $1/k$.

The pH dependence of the plateau rate constant k_{lim} can be used to determine if the reaction shows a dependence on the hydroxide ion concentration. A typical situation is shown in Figure 3. In this case there is a positive intercept so that $k_{lim} = k_0 + k_{OH}[OH^-]$. The k_0 term normally indicates a solvolytic reaction (nucleophilic attack by water) while k_{OH}, the slope of the line, relates to base hydrolysis.

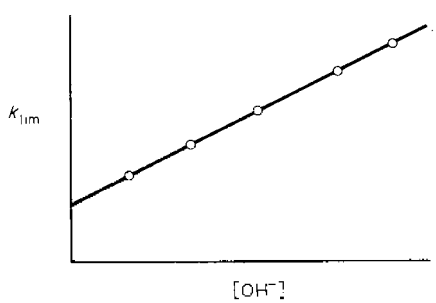


Figure 3

Many additional complexities can occur in reactions of this type due to the presence of more than one complex in solution and to metal-buffer interactions which can lead to additional metal equilibria involving the buffer anion and even to mixed ligand complex formation.

61.4.2 THE HYDROLYSIS OF AMINO ESTERS, AMIDES AND PEPTIDES

61.4.2.1 Labile Metal Systems

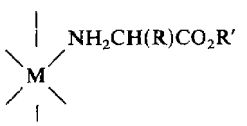
The metal ion-catalyzed hydrolysis of amino acid esters and peptides has been a subject of continuing interest over the past three decades. In the early 1930s the hydrolysis of peptides was

found to be subject to metal ion catalysis, but the discovery by Kroll in 1952 that the hydrolysis of α-amino acid esters was catalyzed by metal ions stimulated considerable interest in the area. Many of these reactions can be considered as simple model systems for such metalloenzymes as carboxypeptidase A, leucine aminopeptidase and glycylglycine dipeptidase.[25]

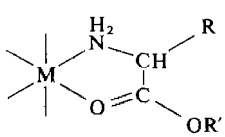
A variety of reviews on various aspects of the topic are available.[22,23,24,28,30] The work carried out has dealt with catalysis by labile metal ions such as Cu^{II} and Ni^{II}, with non-labile Co^{III} systems and with catalysis by Pd^{II} and some rare earth ions. A major problem in studying the hydrolysis of α-amino acid esters in the presence of labile metal ions has been the determination of the ligand binding sites, and the identification of the catalytically active species in solution. Many of the early kinetic studies were carried out with monoamino esters, where the formation constants are quite low. Solutions containing, for example, copper(II) and the ester ligand (E) will contain a variety of complexes such as $[CuE]^{2+}$, $[CuE_2]^{2+}$, $[CuE_3]^{2+}$ and $[CuE_4]^{2+}$. The most abundant species will depend on the copper(II):ester ratio, and inevitably there is more than one complex present. In addition, there will be mixed species $[CuEA]^{+}$, $[CuE_2A]^{+}$, *etc.* formed as the hydrolysis of E to A^{-} (the anion of the amino acid) occurs. As a result, it can be difficult to establish the nature of the hydrolytically most active species.

A number of these difficulties have been overcome by the use of polydentate amino acid derivatives containing additional donor atoms capable of interacting with a metal ion or by using mixed ligand complexes. There has been considerable success in interpreting the kinetic data for such systems. Many of the initial investigations (as with all studies of metal ion-catalyzed reactions) were complicated by the use of complexing buffers which led to additional problems due to metal ion–buffer interactions. The use of pH-states and the advent of non-complexing buffers such as Hepes and Pipes[37] and the new Elias buffers[38] have essentially resolved this problem.

Amino acid esters can be monodentate (**1**) or bidentate (**2**), and examples of both types of complex have been isolated and their solid state IR spectra studied.[39–41] Many investigations have shown that formation of the monodentate ester species has similar effects to protonation of the α-amino group. Thus the pK_a values of $MNH_2CH(R)CO_2H$ and $\overset{+}{N}H_3CH_2CO_2H$ (carboxyl ionization) are usually quite similar.[42]



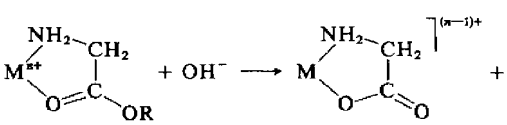
(1)



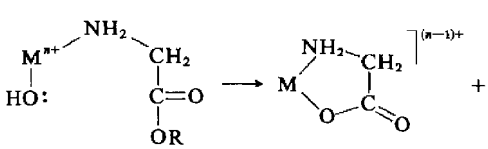
(2)

Essentially three different routes can be considered for the base hydrolysis of an amino acid ester in the presence of a metal ion (equations 8–10). In general terms hydrolysis of the monodentate N-coordinated ester (equation 8) would be expected to be somewhat similar to base hydrolysis

$$M^{n+}\text{—}NH_2CH_2CO_2R + OH^- \rightarrow M^{n+}\text{—}NH_2CH_2CO_2^- + ROH \quad (8)$$

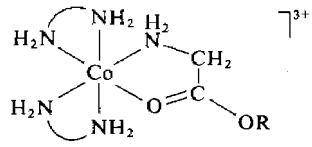


(9)



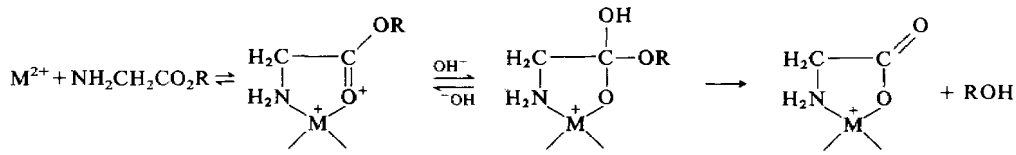
(10)

of $\overset{+}{N}H_3CH_2CO_2R$ (EH^+), and this is generally observed to be the case (see later). Formation of the chelated ester species leads to a considerable reduction[39–41] in the carbonyl stretching frequency, *e.g.* from 1740 to 1600 cm^{-1} in the case of copper(II) indicating significant polarization of the carbonyl group by the metal ion. Kroll[36] initially suggested that such chelated ester species were involved in the metal ion-catalyzed hydrolysis of glycine methyl ester and this view is now supported by much experimental evidence. Such carbonyl-bonded ester species have been characterized in the solid state (Section 61.4.2.2.4), a typical example being the cobalt(III) complex (**3**).[138] Polarization of the carbonyl group by the metal ion assists nucleophilic attack by reagents



(3)

such as OH^-, OH_2 and RNH_2 (Scheme 1). These reactions involve the formation of the tetrahedral intermediate (**4**) and such an intermediate has been detected spectroscopically[43] in the hydrolysis of some cobalt(III) complexes of the type shown in (**3**). Oxygen exchange data are also fully consistent with this view.[44] Presumably in these reactions formation of the tetrahedral intermediate is the rate-determining step.



(4)

Scheme 1 Metal ion-catalyzed hydrolysis of glycine esters

The intramolecular hydrolysis involving coordinated hydroxide (equation 10) was first detected in kinetically inert cobalt(III) complexes and these reactions are considered in detail in Section 61.4.2.2.3.

61.4.2.1.1 Base hydrolysis of amino acid esters

In order to assess the magnitudes of the catalytic effects of metal ions on the hydrolysis of α-amino acid esters, it is necessary to have kinetic data on the base hydrolysis of such compounds.

$$NH_2CHRCO_2R' + OH^- \overset{k_E}{\rightleftharpoons} NH_2CHRCO_2^- + R'OH \quad (11)$$

$$\overset{+}{N}H_3CHRCO_2R' + OH^- \overset{k_{EH^+}}{\rightleftharpoons} \overset{+}{N}H_3CHRCO_2^- + R'OH \quad (12)$$

The reaction scheme can be summarized by equations (11) and (12). The pK_a for the ionization of the α-amino group falls in the range 7 to 7.6.[22] Values of k_E and k_{EH^+} have been determined for a series of α-amino acid esters and typical kinetic data are given in Table 3. Values of k_{EH^+}/k_E are *ca.* 100 for α-amino acid esters. Withdrawal of the amino group to the β-position lowers k_{EH^+}/k_E to about 50 (*e.g.* methyl β-alaninate) and further withdrawal to the ε-position (methyl lysinate) reduces the ratio to 2.7.

61.4.2.1.2 Monoamino esters

Initially studies of metal ion-promoted hydrolysis were centred on simple monoamino esters.[36,44,45] However, many of the initial investigations led to rather conflicting results. These reactions are difficult to study due to the low formation constants of the active complexes. More recent measurements[46–48] have provided rate constants (Table 4) which show only order of magnitude agreement; however, it has been possible to establish that hydroxide ion is the predominant nucleophile at pH values of *ca.* 5. Higher pH values lead to precipitation of metal hydroxides. Evidence for nucleophilic attack by water has also been obtained.[46–48]

The rate enhancements in the copper(II)-glycine ester systems are large (*ca.* 10^5–10^6-fold). These rate accelerations are similar to the rate accelerations of *ca.* 10^6 observed in the inert cobalt(III) systems where direct metal–ester carbonyl bonding occurs. It is thus likely that such hydrolyses occur by the reactions outlined in Scheme 1. However, attack by coordinated hydroxide (equation 10) cannot be excluded and hydrolysis could occur by a combination of both reaction pathways.

Table 3 Rate Constants for the Base Hydrolysis of Amino Acid Esters at 25 °C and $I = 0.1$ M (KCl)[a]

Amino ester	k_E (M^{-1} s^{-1})	k_{EH^+} (M^{-1} s^{-1})	$k_{EH_2^{2+}}$ (M^{-1} s^{-1})
Methyl glycinate	1.28	28.3	
Ethyl glycinate	0.64	22.9	
Methyl α-alaninate	1.11	80.3	
Methyl α-amino-*n*-butyrate	0.39	44.5	
Methyl norvalinate	0.40	40.2	
Methyl norleucinate	0.37	40.8	
Methyl valinate	0.076	—	
Methyl leucinate	0.455	—	
Ethyl leucinate	0.187	—	
Methyl isoleucinate	0.067	—	
Methyl β-alaninate	0.136	6.87	
Methyl serinate	0.99	—	
Methyl β-phenyl-alaninate	0.55	—	
Ethyl β-phenyl-alaninate	0.235	—	
Methyl methioninate	0.77	—	
Methyl trypto-phanate	0.29	—	
Methyl 2,3-diaminopropionate	0.73	57.3	—
Methyl histidinate	0.62	46.5	—
Methyl cysteinate	0.07 (E^-)	1.07 (EH)	3.83 ($EH^{\pm}$)
Methyl lysinate	0.46	1.26	73.5
Ethyl cysteinate	0.04 (E^-)	0.60 (EH)	6.67 ($EH^{\pm}$)

[a] Data taken from ref. 22. Rate constants are not listed for amino acid esters such as methyl 4-amino-*n*-butyrate where lactamization occurs (see ref. 38).
[b] In the case of the cysteine esters, $E^- = {}^-SCH_2CH(NH_2)CO_2R$; $EH = HSCH_2CH(NH_2)CO_2R$; $EH^{\pm} = {}^-SCH_2CH(\overset{+}{N}H_3)CO_2R$

Table 4 Rate Constants for the Metal Ion-promoted Hydrolysis of Methyl Glycinate and Ethyl Glycinate

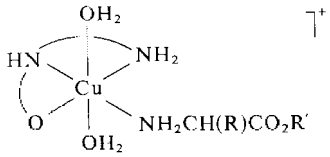
Reaction[a]	*Rate constant (ionic strength, temperature)*	*Ref.*
$CuE^{2+} + OH^-$	7.6×10^4 M^{-1} s^{-1} (0.16 M, 25 °C)	46
$CuE^{2+} + H_2O$	4.3×10^{-5} s^{-1} (0.16 M, 25 °C)	46
$NiE^{2+} + OH^-$[b]	3.98×10^3 M^{-1} s^{-1} (1.0 M, 30 °C)	47
$NiE^{2+} + H_2O$[b]	1.9×10^{-4} s^{-1} (1.0 M, 30 °C)	47
$CuE^{2+} + OH^-$[b]	1.4×10^5 M^{-1} s^{-1} (?, 25 °C)	48
$CuEA^+ + OH^-$[b]	8.4×10^3 M^{-1} s^{-1} (?, 25 °C)	48
$CuE^{2+} + H_2O$[b]	2.5×10^{-5} s^{-1} (?, 25 °C)	48

[a] E is $H_2NCH_2CO_2Me$ or $H_2NCH_2CO_2Et$; A^- is $H_2NCH_2CO_2^-$.
[b] These values refer to glycine ethyl ester.

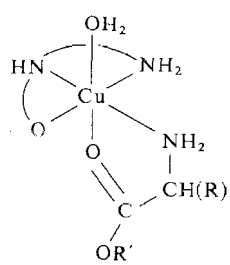
61.4.2.1.3 Mixed ligand complexes of monoamino esters

The measurements made with mixed ligand complexes of palladium(II) illustrate the useful data which can be obtained from mixed ligand complexes containing simple monoamino acid ligands. Angelici and coworkers have studied the hydrolysis of α-amino acid esters in mixed ligand complexes of the type $[CuL\{NH_2CH(R)CO_2R'\}]^{n+}$ using ligands (L) such as iminodiacetate (imda),[49] nitrilotriacetate (nta),[50] 2,2′,2″-tris(aminoethyl)amine (tren),[51] terpyridyl (terpy),[51] diethylenetriamine (dien)[52] and bis(2-pyridylmethylamine) (dpa).[53] Further work by Hay and Banerjee discusses mixed ligand complexes of nta,[54] ethylenediaminemonoacetate (edma),[55] glycylglycine dianion[56] and iminodiacetate (imda).[57] To various degrees these studies can be said to mimic metalloenzyme–substrate complexes.

The chemistry involved can be illustrated by a specific example. Using a ligand such as ethylenediaminemonoacetate,[55] ternary complexes with amino acid esters can be formulated as either (**5**) or (**6**). The ester ligands in the ternary complexes of $edma^-$ undergo base hydrolysis some 10^3 times faster than the free unprotonated esters, although considerably lower effects occur with methyl L-histidinate (Table 5). The magnitude of these effects suggests that the amino acid



(5)



(6)

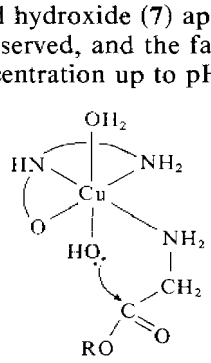
Table 5 Catalytic Effects for the Hydrolysis of the Mixed Ligand Complexes $[Cu(edma)(NH_2CH(R)CO_2R')]^+$ at 25 °C and $I = 0.1$ M (KNO_3)[a]

Ester	$10^{-3}\ k_{OH}$ (*complex*) ($M^{-1}\ s^{-1}$)	k_{OH} (*ester*) ($M^{-1}\ s^{-1}$)	*Ratio*
GlyOMe	1.71	1.28	1.34×10^3
L-β-PheOMe	0.99	0.55	1.18×10^3
GlyOEt	0.63	0.64	1.0×10^3
L-α-AlaOEt	0.59	0.55	1.1×10^3
L-β-PheOEt	0.38	0.24	1.6×10^3
L-HisOMe	0.025	0.62	40

[a] Data taken from R. W. Hay and P. K. Banerjee, *J. Chem. Soc., Dalton Trans.*, 1980, 2452.

ester ligand is probably bidentate with a rather weak alkoxycarbonyl interaction (**6**). A weak interaction is expected for the Jahn–Teller-distorted d^9 configuration of copper(II).

Intramolecular attack by coordinated hydroxide (**7**) appears unlikely in this system in view of the relatively low rate accelerations observed, and the fact that the reaction shows a first order dependence on the hydroxide ion concentration up to pH 8.



(7)

Activation parameters have been determined[58] for the hydrolysis of α-amino acid esters in mixed ligand complexes (Table 6). For base hydrolysis of the complex $[Cu(nta)(NH_2CH_2CO_2Et)]^-$, $\Delta H^{\ddagger} = 20.5$ kJ mol^{-1} and $\Delta S^{\ddagger} = -138$ J K^{-1} mol^{-1}. Catalysis in this system is primarily due to a substantial decrease in $\Delta H^{\ddagger}$ (by *ca.* 21 kJ mol^{-1}) compared with the free ligand. A detailed discussion of the activation parameters is available.[58]

Table 6 Activation Parameters for the Hydrolysis of Methyl Glycinate in the Presence of Metal Nitriloacetates and Tetradentate Nickel(II) Chelates at $I = 0.1$ M[a]

Complex	$log\ K_L$	k_{OH}, 25 °C ($M^{-1}\ s^{-1}$)	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
$[Ni(tren)(GlyOMe)]^{2+}$	14.8	67.1	14.2 ± 3.3	−163 ± 8
$[Ni(trien)(GlyOMe)]^{2+}$	14.0	53.1	30.1 + 2.9	−109 ± 4
[Ni(edda)(GlyOMe)]	13.5	41.2	20.1 + 3.3	−146 ± 8
[Ni(nta)(GlyOMe)]	11.47	52.3	3.8 ± 2.9	−197 ± 8
[Co(nta)(GlyOMe)]	10.81	18.6	6.3 ± 3.3	−201 ± 8
[Cu(nta)(GlyOMe)]	13.05	460	14.2 ± 5.0	−159 ± 13
[Zn(nta)(GlyOMe)]	10.44	34.6	16.7 ± 2.9	−159 ± 8
Cu(nta)(GlyOEt)]	13.05	78.2	20.5	−138

[a] The data are taken from the compilation given by D. E. Newlin, M. A. Pellack and R. Nakon, *J. Am. Chem. Soc.* 1977, **99**, 1078.

An interesting correlation has been observed[53] between the formation constant K_{CuL} of the metal complex and its catalytic activity in a mixed ligand with an amino acid ester. Large values of K_{CuL} (equation 13) lead to lower base hydrolysis rates in the ternary complex. The Lewis

$$Cu^{2+} + L \overset{K_{CuL}}{\rightleftharpoons} CuL^{2+} \tag{13}$$

acidities of the CuL^{n+} complexes decrease as the formation constant for CuL^{n+} increases (Table 7). Strong σ-donors such as tren greatly decrease the Lewis acidity of copper(II). In addition the effects of charge on these reactions do not appear to be of great importance. Thus [Cu(edma)(GlyOMe)]$^+$ undergoes slower base hydrolysis than [Cu(imda)(GlyOMe)], while the hydrolysis of [Cu(dpa)(GlyOMe)]$^{2+}$ is some 10 times slower than the edma derivative. Any electrostatic facilitation of the reaction seems to be overshadowed by changes in the Lewis acidity of copper(II). However, it should be appreciated that these conclusions assume that complexes all react by a similar mechanism.

Table 7 Rate Constants (k_{OH}) and Equilibrium Constants (log K_{CuL}) Associated with the CuL-promoted Hydrolysis of Methyl Glycinate at 25 °C

[CuL(GlyOMe)]	K_{OH} ($M^{-1}s^{-1}$)	*log* K_{CuL}	*Ref.*
[Cu(imda)(GlyOMe)]	7.6×10^3 [a]	10.63	51
[Cu(edma)(GlyOMe)]$^+$	1.7×10^3 [a]	13.29	55
[Cu(nta)(GlyOMe)]$^-$	4.6×10^2 [b]	13.10	50
[Cu(terpy)(GlyOMe)]$^{2+}$	2.2×10^2 [c]	13.40	51
[Cu(dpa)(GlyOMe)]$^{2+}$	1.7×10^2 [c]	14.4	53
[Cu(dien)(GlyOMe)]$^{2+}$	1.4×10^2 [a]	15.9	52
[Cu(tren)(GlyOMe)]$^{2+}$	1.3 [c]	18.8	51

[a] $I = 0.1$ M.
[b] $I = 0.07$ M.
[c] $I = 0.05$ M.

The results are of some significance as far as metalloenzymes are concerned as the Lewis acidity of the metal ion can presumably be 'tailored' to a degree by the appropriate degree of σ-donation and π-acceptance. For the bonding of Zn^{II} to apocarboxypeptidase a value of log K of 10.5 has been estimated[59] and a similar value has been reported[60] for Zn^{II} with apocarbonic anhydrase. Such considerations may be of relevance in determining metal ion specificities of metalloenzymes. Metal ions with high binding constants for apoenzymes may be poor Lewis acid catalysts.

Walker and Nakon[61] have determined values of k_{OH} and the appropriate activation parameters for the base hydrolysis of a series of mixed ligand complexes [Cu(L)(GlyOMe)]$^{x+}$ where L is a tetradentate or tridentate ligand. Tridentate and tetradentate chelates fall on different isokinetic lines suggesting different hydrolytic mechanisms. Both the strengths of the donor atoms of the auxiliary ligands and the charge carried by the complex are of importance in determining the hydrolysis rates. Some related studies have also been published.[62] Correlations have been observed[63] between λ_{max} values for tridentate copper(II) chelates and both log k_{OH} for base hydrolysis of [Cu(L)(GlyOMe)]$^{x+}$ and log K_{OH} for the equilibrium (14). The formation constants K_{CuL} (equation 13) were used as a measure of the Lewis acidity of the various complexes $[CuL]^{x+}$. Some representative data are given in Table 8.

$$[CuL]^{x+} + OH^- \overset{K_{OH}}{\rightleftharpoons} [CuL(OH)]^{(x-1)+} \tag{14}$$

61.4.2.1.4 Bidentate and polydentate esters

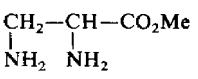
The metal ion-promoted hydrolysis of a number of bidentate esters such as methyl 2,3-diaminopropionate (**8**), methyl histidinate (**9**), methyl cysteinate (**10**) and the ethyl ester of ethylenediaminemonoacetate (**11**) have been studied. The first three esters give very thermodynamically stable metal complexes in solution with pendant ester functions.[64–71] Typical kinetic data for these systems are given in Tables 9 and 10.

Base hydrolysis of the L-(+)-histidine methyl ester complexes[72] follows the reactivity order $[CuE_2]^{2+} > [NiE_2]^{2+} > [CuE]^{2+} > [NiE]^{2+} > EH > CuEA > [CuEOH]^+ > [NiEA]^+ > E$ at 25 °C ($I = 0.1$ M) where E is the ester and A^- is L-histidinate. The bis complex of methyl histidinate

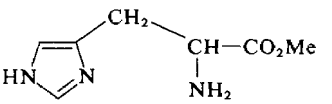
Table 8 Formation Constants for Hydroxo Complex Formation by $[CuL]^{x+}$ Complexes (K_{OH}), Second Order Rate Constants (k_{OH}) for Base Hydrolysis of $[CuL(GlyOMe)]^{x+}$ and λ_{max} Values for $[CuL]^{x+}$ [a]

CuL	*log* k_{OH}	*log* K_{OH}	λ_{max} (nm)
$[Cu(tren)]^{2+}$	0.95	4.44	860
$[Cu(dtma)]^{+}$	0.83	4.25	710
[Cu(paa)]	2.25	4.34	670
[Cu(nta)]	2.50	4.20	775
$[Cu(dpa)]^{2+}$	2.06	5.05	637
$[Cu(dien)]^{2+}$	1.39	4.67	611
$[Cu(terpy)]^{2+}$	2.28	5.71	680
[Cu(lmda)]	4.50	6.26	730

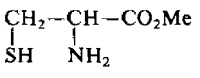
[a] Data from J. K. Walker and R. Nakon, *Inorg. Chem. Acta*, 1981, **55**, 135.



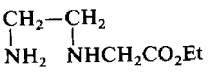
(8)



(9)



(10)



(11)

Table 9 Rate Constants k_{OH} for the Metal Ion-promoted Base Hydrolysis of some Bidentate Amino Acid Ester Species at 25 °C

System	k_{OH} *for complexes*[a] ($M^{-1}\,s^{-1}$)				*Ref.*
	ME_2^{2+}	MEA^{+}	ME^{2+}	$ME(OH)^{+}$	
Cu^{II}-L-methyl histidinate	198.8[b]	—	—	—	67
	328	42.7	175	33.7	72
Ni^{II}-L-methyl histidinate	118	16.5	78.3	—	84
	37.5[b]	—	322.5	—	67
	188.3	28.3	87.7	—	72
Cu^{II}-D, L methyl 2,3-diaminopropionate	305	88.7	618	135	73
Hg^{II}-D, L-methyl 2,3-diaminopropionate	115	24.3	82	50	73

[a] All rate constants refer to base hydrolysis at 25 °C and $I = 0.1$ M unless otherwise stated.
[b] $I = 0.16$ M.

Table 10 Rate Constants for the Metal Ion-promoted Base Hydrolysis of some Bidentate Species of Cysteinate Esters at 25 °C

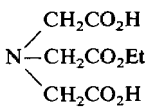
System	k_{OH} *for complexes* [a] ($M^{-1}\,s^{-1}$)		*Ref.*
	ME_2	MEA^{-}	
Ni^{II}-L-methyl cysteinate	10.8	3.6	71
Pb^{II}-L-methyl cysteinate	5.7	0.97	71
Zn^{II}-L-methyl cysteinate	4.7	1.38	71
Cd^{II}-L-methyl cysteinate	3.5	0.7	71
Hg^{II}-L-methyl cysteinate	2.3	0.77	71
Ni^{II}-L-ethyl cysteinate	2.6[(b)]		67
Zn^{II}-L-ethyl cysteinate	1.9[(b)]		67
Cd^{II}-L-ethyl cysteinate	1.05[(b)]		67

[a] All rate constants refer to base hydrolysis at 25 °C and $I = 0.1$ M unless otherwise stated.
[b] $I = 0.16$ M.

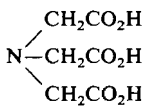
with copper(II) (CuE_2^{2+}) hydrolyzes some 265-fold more rapidly than the unprotonated ester (E) when the appropriate statistical corrections are made. The protonated ester (EH^+) hydrolyzes some 75 times more rapidly than E. The rate accelerations are relatively low as the metal ion does not interact with the alkoxycarbonyl group of the ester. In these complexes, electrostatic effects due to the positive charge(s) carried by the species appear to be of prime importance in determining hydrolysis rates.

Similar considerations apply to complexes of methyl 2,3-diaminopropionate.[73] Thermodynamic parameters ΔH^+ and ΔS^+_{298} for the base hydrolysis of the $[CuE_2]^{2+}$ and $[CuEA]^+$ complexes of methyl L-histidinate[72] and methyl DL-2,3-diaminopropionate[73] indicate that ΔH^+ values are *ca.* 4–8 kJ mol^{-1} higher for the metal complexes compared with the free ligands. The rate increases are due to more positive values of ΔS^+_{298} for the complexes.

Angelici and his coworkers have overcome some of the practical problems arising from the low formation constants of simple monoamino esters, by incorporating the ester moiety into a larger polydentate ligand. A typical example is the use of ethyl glycinate-*N,N*-diacetic acid (**12**) which hydrolyzes to give nitrilotriacetic acid (**13**).

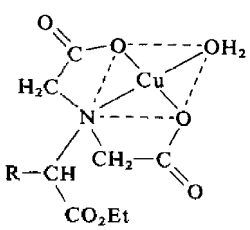


(**12**)

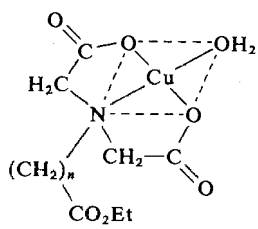


(**13**)

Kinetic measurements have been reported[74–76] for ligands involving ethyl glycinate (**14a**), ethyl alaninate (**14b**), ethyl valinate (**14c**), ethyl leucinate (**14d**), butyl glycinate, ethyl β-alaninate (**15a**) and ethyl 4-aminobutyrate (**15b**). Metal ion-promoted hydrolysis has been studied using a variety of metal ions (Cd^{II}, Ni^{II}, Mn^{II}, Fe^{II}, Co^{II}, Zn^{II}, Pb^{II}, La^{III}, Nd^{III}, Gd^{III}, Dy^{III}, Er^{III}, Yb^{III}, Lu^{III} and Sm^{III}) for a few of these ligands. The 1:1 complexes have large formation constants and display little tendency to add a second ligand. However, hydroxo complexes are formed at higher pH due to deprotonation of water molecules.



(**14**) **a**; R = H
b; R = Me
c; R = $CHMe_2$
d; R = CH_2CHMe_2



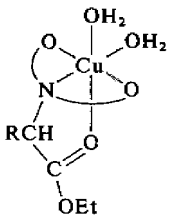
(**15**) **a**; $n = 2$
b; $n = 3$

The ethyl glycinate-*N,N*-diacetic acid derivative (**12**) may be used to illustrate the general features of these reactions. Hydrolysis of the copper(II) complex in the pH range 5–7, studied by pH-stat, corresponds to equation (15) where $EGDA^{2-}$ = ethyl glycinate-*N,N*-diacetate and

$$[Cu(EGDA)] + OH^- \rightarrow [Cu(NTA)]^- + EtOH \quad (15)$$

NTA^{3-} = nitrilotriacetate. The rate expression takes the form, rate = $k_{OH}[Cu(EGDA)][OH^-]$ with $k_{OH} = 2.18 \times 10^4\ M^{-1}\ s^{-1}$ at 25 °C.[74] The kinetic measurements do not differentiate between bimolecular hydroxide ion attack on the 1:1 aqua chelate (**14a**) and intramolecular attack by coordinated hydroxide (*ca.* 0.01 to 20% of $[Cu(EGDA)(OH)]^-$ exists in solution in the pH range 5.0–7.0). Attack by coordinated hydroxide does not appear to be favoured in this system due to the relative dispositions of the hydroxide ion and the alkoxycarbonyl group. The hydrolytic reactions are very rapid, with rate accelerations similar to those observed with copper(II) and methyl glycinate, suggesting that in aqueous solution there is a direct interaction between the metal ion and the alkoxycarbonyl group as shown in (**16**).

Rodgers and Jacobson[77] have published the crystal structure of DL-(ethyl valinate-*N,N*-diacetato)diaquacopper(II), the copper(II) complex of EVDA (**14c**). The stereochemistry around copper is distorted octahedral, the equatorial coordination sphere consisting of the tertiary



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nitrogen, the two acetate oxygens and a water molecule. The second water molecule occupies an axial position at a greater distance from the metal, while the ether oxygen of the ester group occupies the opposite axial position lying at 2.84 Å from the metal. The ester carbonyl group is not coordinated in the solid state. This system provides a good example of some of the difficulties involved in defining the nature of catalytically active species of labile complexes in solution.

Kinetic data for the base hydrolysis of a variety of metal complexes of EGDA are summarized in Table 11. Rare earth ions such as Yb^{III} and Lu^{III} have very marked catalytic effects, and these systems provide one of the few examples of detailed studies of rare earth catalysis. Activation parameters have been obtained (Table 12) and these show some interesting variations. In complexes of nickel(II), copper(II) and lead(II), the rate accelerations are due primarily to a lowered $\Delta H^{\ddagger}$ with little change in $\Delta S^{\ddagger}$ compared with the free ligand. For rare earth ions quite the reverse is observed with more positive (*i.e.* less negative) $\Delta S^{\ddagger}$ values leading to the rate enhancement with no change in $\Delta H^{\ddagger}$. Different mechanisms appear to operate in the two systems. Nucleophilic catalysis (by acetate, HPO_4^{2-}, pyridine, 4-picoline and nitrite) of some of these reactions has been studied[75] using esters derived from ethyl valinate and ethyl leucinate which are sterically hindered to base hydrolysis.

Table 11 Rate Constants for the Base Hydrolysis of Metal Complexes of Ethyl Glycinate-*N,N*-Diacetate at 25 °C[a]

Metal ion	$10^{-2}k$ ($M^{-1}s^{-1}$)	*Metal ion*	$10^{-2}k$ ($M^{-1}s^{-1}$)
Cd^{II}	2.14	La(III)	115
Ni^{II}	3.89	Nd(III)	347
Mn^{II}	4.18	Sm(III)	447
Co^{II}	10.1	Gd(III)	376
Fe^{II}	38.6	Dy(III)	877
Zn^{II}	66.2	Er(III)	1920
Cu^{II}	218	Yb(III)	3460
Pb^{II}	283	Lu(III)	3450

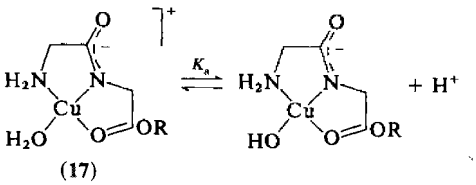
[a] Data from B. E. Leach and R. J. Angelici, *J. Am. Chem. Soc.*, 1968, **90**, 2504. $I = 0.05$ M (KNO_3), $[M] = [EGDA] = 6.7 \times 10^{-4}$ M.

Table 12 Activation Parameters for the Base Hydrolysis of Ethyl Glycinate and Metal Complexes of Ethyl Glycinate-*N,N*-Diacetate[a]

Ester	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
Ethyl glycinate	44.4±2.1	−90.8±4.2
Betaine ethyl ester	40.6±1.3	−77.4±4.6
[Cu(EGDA)]	20.9±2.1	−91.6±6.3
[Ni(EGDA)]	23.8±1.7	−101.3±5.0
[Pb(EGDA)]	18.4±2.5	−98.3±8.8
$[Sm(EGDA)]^+$	41.8±1.7	−16.7±5.0
$[Lu(EGDA)]^+$	42.7±2.5	+3.3±8.4

[a] Data for the metal complexes taken from B. E. Leach and R. J. Angelici, *J. Am. Chem. Soc.*, 1968, **90**. 2504.

The copper(II)-catalyzed hydrolysis of the methyl esters of glycylglycine and glycylsarcosine has been studied,[78] as has the copper(II)-promoted hydrolysis of ethyl glycylglycinate, ethyl glycyl-β-alaninate and ethyl glycyl-L-leucinate.[79] Under the conditions of the experiments (pH > 7.0) the peptide esters act as tridentate ligands, donation occurring from the terminal amino group and the deprotonated amide nitrogen atom with a weak interaction between the metal ion and the carbonyl group of the ester (**17**). Rate accelerations of the order of 10^3 (compared with the



(17)

unprotonated ligands) were observed (Table 13). Analogous studies have been carried out with Pd^{II} complexes[80] but in this case much higher rate accelerations (*ca.* 10^5) are observed. Nakon and Angelici[81] have carried out a potentiometric and IR study of copper(II) complexes of glycylglycine methyl ester and glycylsarcosine methyl ester in an attempt to define the nature of the active complexes in aqueous solution.

Table 13 Rate Constants and pK_a Values for the Base Hydrolysis of some Copper(II) Complexes of Dipeptide Esters at 25 °C and $I = 0.01$ M[a]

Ligand	pK_a	k_{OH}[b] ($M^{-1}s^{-1}$)	k_{OH}[c] ($M^{-1}s^{-1}$)
Ethyl glycylglycinate	8.0	2.87×10^3	1.98×10^2
Ethyl glycyl-β-alaninate	9.1	1.36×10^2	1.51×10^1
Ethyl glycyl-L-leucinate			1.68×10^2

[a] Data taken from R. W. Hay and K. B. Nolan, *J. Chem. Soc., Dalton Trans.*, 1974, 2542.
[b] Base hydrolysis of the aqua complex.
[c] Base hydrolysis of the hydroxo complex.

Base (and water) hydrolysis of the 1 : 1 complex of the tetramethyl ester of EDTA with copper(II) ($[Cu(Me_4EDTA)]^{2+}$) has been investigated.[82] In the complex probably two ester groups of the ligand are bonded to the metal ion in conjunction with the two nitrogen donors. Rate accelerations of the order of 10^5 were observed in base hydrolysis compared with the unprotonated ligand (Table 14). A variety of metal complexes of the ligand have also been isolated and characterized.[83]

Table 14 Rate Constants for the Base Hydrolysis of EDTA Methyl Esters and their Copper(II) Complexes at 25 °C and $I = 0.1$ M[a]

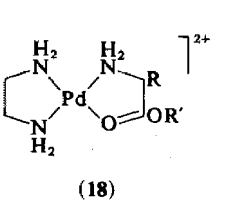
Ligand	k_{OH} ($M^{-1}s^{-1}$)	*Complex*	k_{OH} ($M^{-1}s^{-1}$)	*Rate enhancement*
Me_4edta	2.10	$Cu(Me_4edta)^{2+}$	3.2×10^5	1.6×10^5
Me_3edta^-	0.86	$Cu(Me_3edta)^+$	8.0×10^4	8.0×10^4
Me_2edta^{2-}	0.35	$Cu(Me_2edta)$	1.5×10^3	4.4×10^3
$Meedta^{3-}$	0.06	$Cu(Meedta)^-$	7.5×10^1	1.2×10^3

[a] Data taken from R. W. Hay and K. B. Nolan, *J. Chem. Soc., Dalton Trans.*, 1975, 1348.

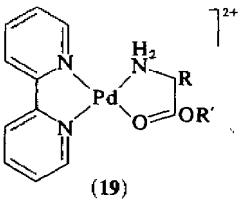
61.4.2.1.5 Palladium(II) complexes

A number of recent studies have been carried out with palladium(II) complexes,[85–87] of the types (**18**) and (**19**). These mixed ligand complexes are formed in solution by the addition of the α-amino acid ester to the corresponding diaqua species, for example $[Pd(en)(OH_2)_2]^{2+}$. The kinetics of hydrolysis of the ester ligand in such mixed ligand complexes have been studied in detail. Nucleophilic attack by both OH^- and OH_2 occurs. Typical kinetic data are summarized in Table 15.

Substantial rate accelerations are observed in these systems for base hydrolysis. Thus for the ethylenediamine complex (**18**) rate increases of 4×10^4 for GlyOEt to 1.4×10^7 for ethyl picolinate are observed.[85] These rate accelerations are consistent with the formation of carbonyl-bonded species (**18**). The effects with methyl L-cysteinate and methyl L-histidinate are much less marked as such ligands can give mixed ligand complexes which do not involve alkoxycarbonyl donors. Thus in the case of methyl L-histidinate the complex (**20**) is formed. For these latter two esters only relatively small rate accelerations of 20–100 occur. For the chelate ester complexes, the ratios of k_{OH}/k_{H_2O} fall within the range 3.8×10^9 to 3.2×10^{11}. Such values for the relative nucleophilicity of water and hydroxide ion are comparable with those previously noted for copper(II) complexes.[82]



(18)



(19)

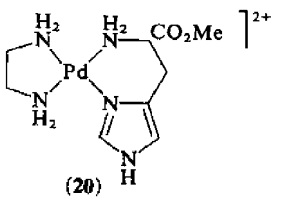
Table 15 Hydrolysis Data for $[Pd(en)(NH_2CH(R)CO_2R')]^{2+}$ Complexes at 25 °C and $I = 0.1$ M (KNO_3)[a]

Ester	k_{OH} (*complex*) ($M^{-1}\,s^{-1}$)	k_{H_2O} (*complex*) ($M^{-1}\,s^{-1}$)	k_{OH} (*ester*) ($M^{-1}\,s^{-1}$)
GlyOEt	2.45×10^{4}	5.3×10^{-6}	0.64
GlyOMe	6.25×10^{4}	4.9×10^{-6}	1.28
α-AlaOEt	6.15×10^{4}	1.6×10^{-5}	0.55
PheOEt	11.75×10^{4}	1.04×10^{-5}	0.24
CysOEt	4.20	5.17×10^{-6}	0.04
HisOMe	12.76	5.48×10^{-6}	0.62
picOEt[b]	6.47×10^{6}	2.05×10^{-5}	0.46

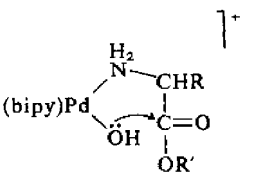
[a] Data taken from R. W. Hay and P. Banerjee, *J. Chem. Soc., Dalton Trans.*, 1981, 362.
[b] picOEt = ethyl picolinate (2-carbethoxypyridine).

Although intramolecular attack by coordinated hydroxide ion (**21**) could occur in these systems, this pathway in not supported by the experimental evidence.[86]

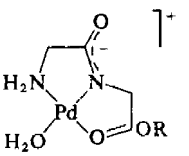
The palladium(II)-promoted hydrolysis of methyl glycylglycinate and isopropyl glycylglycinate has been investigated over a temperature range.[80] Complexes of type (**22**) are formed in which the amino, deprotonated amide and alkoxycarbonyl groups act as donors. Hydrolysis by both H_2O and OH^- ion is observed. Base hydrolysis of the coordinated peptide esters is *ca.* 10^5-fold faster than the unprotonated peptide esters.



(20)



(21)

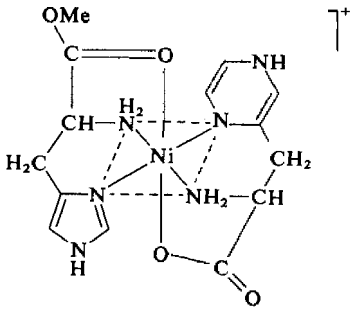


(22) R = Me or Pr^i

61.4.2.1.6 Kinetic stereoselectivity

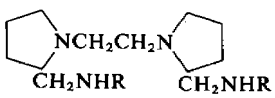
The general topic of stereoselectivity in metal complexes of amino acids and their derivatives has been reviewed.[88] Stereoselective effects have been observed in the base hydrolysis of some mixed ligand complexes involving amino acid esters. The complex [Ni(D-HisOMe)(L-His)]$^+$ undergoes base hydrolysis[89–91] some 40% faster than [Ni(D-HisOMe)(D-His)]$^+$. Stereoselectivity is not observed for the analogous copper(II) complexes.[90,91] The formation constants of the diastereoisomeric nickel complexes are identical,[89] so that a kinetic stereoselective effect must operate. The $[NiEA]^+$ complex (A^- = the amino acid anion, E = the amino acid ester) probably involves tridentate A^- and primarily bidentate E. The octahedral coordination of nickel(II) results in the possibility of a direct interaction between metal ion and ester carbonyl (**23**). Such an interaction can only occur when the two ligands are of opposite configurations as a *trans* arrangement of the bulky imidazole donors is preferred.[92–95] The interaction must be very weak in view of the small rate differences between the diastereoisomers. Such transient coordination is less likely for copper(II), which favours a tetragonal geometry. In the complex $[CuEA]^+$, both E and A^- are probably bidentate with possibly weak apical carboxylate coordination with A^-.

More detailed studies of reactions of this type have been reported.[96,97] Nickel(II) complexes of histidine and tryptophan provide stereoselectivity in the hydrolysis of histidine methyl ester, but stereoselectivity is not observed with nickel(II) complexes of aspartic acid or methionine. Only tridentate ligands with a minimum steric bulk appear to be capable of exhibiting stereoselectivity in reactions of this type.



(23)

The coordination of optically active amino acids and their methyl esters to nickel(II) complexes of 1,2-bis(2-(*S*)-aminomethyl-1-pyrrolidinyl)ethane (**24**; R = H) and 1,2-bis(2-(*S*)-*N*-methylaminomethyl-1-pyrrolidinyl)ethane (**24**; R = Me) has been studied.[98] Some amino acidate ions coordinate stereoselectivity, as do their methyl esters, so that base hydrolysis of the esters proceeds stereoselectively.



(24)

Hatano and Nozawa[99] have observed stereoselective effects in the hydrolysis of D- and L-phenylalanine esters using poly-L-lysinecopper(II) complexes as catalysts and some aspects of the topic have been reviewed.[99]

61.4.2.1.7 Hydrolysis of amino acid amides and peptides

A variety of metal ions, *i.e.* nickel(II),[100,101] copper(II),[102] cobalt(II)[103] and palladium(II),[104,105] promote the ionization of peptide (or amide) hydrogens and the topic has been reviewed.[106] Promotion of peptide hydrogen ionization increases in the series $Co^{II} < Ni^{II} < Cu^{II} < Pd^{II}$.[104] A number of bisdipeptide-cobalt(III) complexes containing deprotonated amide groups have been investigated and their spectral properties studied.[107-109] Protonation in acidic media occurs on oxygen rather than nitrogen to give the iminol tautomer of the dipeptide ligand.[109,110] Many studies have shown that the oxygen atom is the site of both protonation and metal ion coordination to the neutral amide function, while the nitrogen atom becomes the metal bonding site when ionization of an amide hydrogen occurs. A number of discussions are available on the general topic of metal peptide complexes[106,107,111-115] and the subject is currently reviewed.[28]

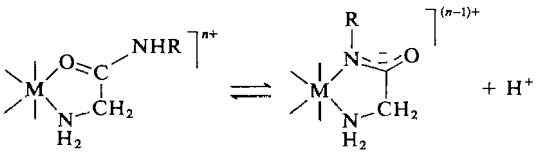
Early work[116] established that Cu^{II}, Ni^{II} and Co^{II} promote the hydrolysis of glycinamide in the pH range 9.35 to 10.35 at temperatures of 6.5 to 75 °C. Bamann and his collaborators carried out an extensive series of studies on the metal ion-promoted hydrolysis of peptides and related compounds[117] and a review of this early work is available.[118] Highly charged ions such as thorium(IV) were found to promote the hydrolysis of leucylglycylglycine at pH values as low as 5. The thorium(IV) species is very extensively hydrolyzed at this pH and the reaction is presumably heterogeneous. Gel hydrolysis is effective at relatively low temperatures (37 °C), whereas observable effects were only obtained with such ions as copper(II) at temperatures of *ca.* 70 °C.

Bamann *et al.*[119] also found that the hydrolysis of di- and tri-peptides is catalyzed by rare earth ions at pH 8.6. Cerium(IV) and Ce^{III} were particularly effective even at a temperature of 37 °C. The same reactions with La^{III} as a catalyst were much slower and only occurred at an appreciable rate at 70 °C. Many of these reactions merit further study.

The copper(II)-promoted hydrolysis of glycylglycine has been studied in some detail.[120] Copper(II) ions catalyze the hydrolysis of glycylglycine in the pH range 3.5 to 6 at 85 °C.[120] The pH rate profile has a maximum at pH 4.2, consistent with the view that the catalytically active species in the reaction is the carbonyl-bonded complex. The decrease in rate at higher pH is associated with the formation of a catalytically inactive complex produced by ionization of the peptide hydrogen atom. This view has subsequently been confirmed by other workers,[121] in conjunction with an IR investigation of the structures of the copper(II) and zinc(II) complexes in D_2O solution.[122] Catalysis by cobalt(II),[123] and zinc(II), nickel(II) and manganese(II) has also been studied.[124-126]

Copper(II) has been found to inhibit the hydrolysis of glycylglycine in basic solution (pH > 11).[127] Conley and Martin[128] have also found that, at pH values in excess of 11, copper(II) inhibits the hydrolysis of glycinamide due to amide hydrogen ionization. Similar results were obtained with picolinamide, and a bis-picolinamide complex of nickel(II) containing deprotonated amide groups was isolated.[128]

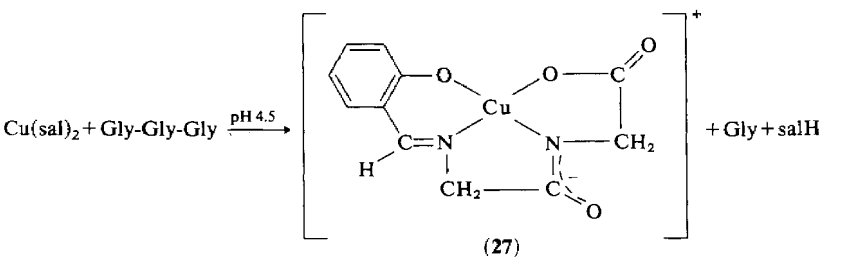
The above studies indicate that metal ions catalyze the hydrolysis of amides and peptides at pH values where the carbonyl-bonded species (**25**) is present. At higher pH values where deprotonated complexes (**26**) can be formed the hydrolysis is inhibited. These conclusions have been amply confirmed in subsequent studies involving inert cobalt(III) complexes (Section 61.4.2.2.2). Zinc(II)-promoted amide ionization is uncommon, and the first example of such a reaction was only reported in 1981.[103] Zinc(II) does not inhibit the hydrolysis of glycylglycine at high pH, and amide deprotonation does not appear to occur at quite high pH values. Presumably this is one important reason for the widespread occurrence of zinc(II) in metallopeptidases. Other metal ions such as copper(II) would induce amide deprotonation at relatively low pH values leading to catalytically inactive complexes.



(**25**) active (**26**) inactive

Polarization of the carbonyl group by the metal ion in the carbonyl-bonded complex (**25**) promotes nucleophilic attack at the carbonyl carbon by nucleophiles such as hydroxide ion and water.

An interesting metal-promoted peptide hydrolysis has been observed during an investigation of Schiff base complexes of copper(II) with glycine, diglycine and triglycine.[129] Diglycine reacts with bis(salicylaldehydato)copper(II) and bis(benzoylacetaldehydato)copper(II) to give the glycylglycinato Schiff base copper(II) complexes. A similar reaction with triglycine at pH 4.5 gave, however, the copper(II) complex of the diglycine Schiff base (**27**; Scheme 2) and free glycine. Subsequent work[130] has shown that hydrolytic cleavage occurred at the carboxyl end of the tripeptide, although not with 100% specificity.



(**27**)

Scheme 2

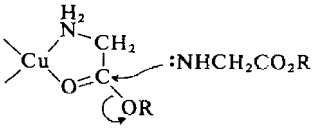
The reactions of $Cu(sal)_2$ (sal = salicylaldehyde monoanion) with glycinamide, glycine esters and the amide and esters of glycylglycine have been studied[131] and the crystal structure of *N*-salicylideneglycinatoaquacopper(II) tetrahydrate has been determined.[132] Reactions of this type merit detailed kinetic study. It should be possible to develop useful peptide-cleaving reagents using reactions of this general type.

61.4.2.1.8 Peptide bond formation

Peptide bond formation using non-labile cobalt(III) complexes has now been developed to a useful synthetic level (Section 61.4.2.2.4), but few attempts have been made to use other metal centres. The formation of glycine peptide esters in the presence of copper(II) has been noted.[133] Treatment of glycine esters with copper(II) (other metal ions can also be used) in a non-aqueous solvent at room temperature gave di-, tri- and tetra-glycine peptide esters. After carbobenzyloxylation, the peptide esters were separated by column chromatography, and no evidence was obtained

for diketopiperazine formation. The polymerization of the methyl esters of amino acids *via* their copper(II) complexes has also been reported.[134]

Presumably these reactions involve intermediates of type (**28**) which undergo nucleophilic attack by a molecule of the ester leading initially to dipeptide ester complexes. These complexes then undergo further reactions of a similar type.



(**28**)

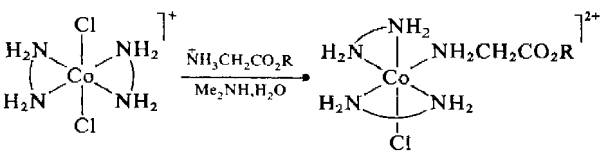
61.4.2.2 Non-labile Cobalt(III) Complexes

The use of kinetically inert cobalt(III) complexes has led to important developments in our understanding of the metal ion-promoted hydrolysis of esters, amides and peptides. These complexes have been particularly useful in helping to define the mechanistic pathways available in reactions of this type. Work in this area has been the subject of a number of reviews.[21–24] Although most of the initial work was connected with cobalt(III), investigations are now being extended to other kinetically inert metal centres such as Rh^{III}, Ir^{III} and Ru^{III}.

It is convenient to discuss these reactions under the following headings: ester hydrolysis, peptide (amide) hydrolysis and peptide bond formation; but it should be remembered that similar intermediates occur in each case and the discussion overlaps the three sections.

61.4.2.2.1 Ester hydrolysis

Alexander and Busch[135] first described the preparation of complexes of the type *cis*-$[Co(en)_2(CH_2CH_2CO_2R)Cl]Cl_2$ (**29**) by reacting the appropriate amino acid ester hydrochloride with *trans*-$[Co(en)_2Cl_2]Cl$ in aqueous solution, the free amino acid ester being generated *in situ* by the presence of a weakly coordinating base such as Me_2NH.



(**29**)

Hydrolysis of the N-coordinated amino acid ester complexes with 4 M HCl leads to the corresponding complexes containing the N-coordinated amino acid.[136]

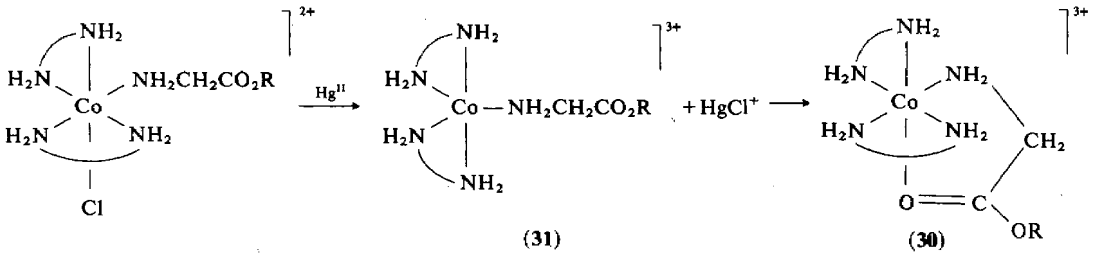
Mercury(II)-promoted hydrolysis[137] of *cis*-$[Co(en)_2X(GlyOR)]^{2+}$ in acidic solution (equation 16) gives $[Co(en)_2(Gly)]^{2+}$, and it was suggested that a chelated ester species $[Co(en)_2(GlyOR)]^{3+}$ (**30**) was the reactive intermediate in the Hg^{II}-promoted reaction (Scheme 3).

$$cis\text{-}[Co(en)_2X(GlyOR)]^{2+} + Hg^{2+} + H_2O \rightarrow [Co(en)_2(Gly)]^{2+} + ROH + H^+ + HgX^+ \quad (16)$$

(X = Cl, Br; R = Me, Et, Pr^i)

Evidence in support of this mechanism was provided by changes in the C=O stretching frequency as the monodentate ester (1735 cm^{-1}) was first chelated (1610 cm^{-1}) and then hydrolyzed to $[Co(en)_2(Gly)]^{2+}$ (1640 cm^{-1}). The reaction presumably proceeds *via* the five-coordinate species (**31**), and the ester carbonyl oxygen competes so effectively with solvent water for the vacant coordination site that the chelate ester is formed exclusively.

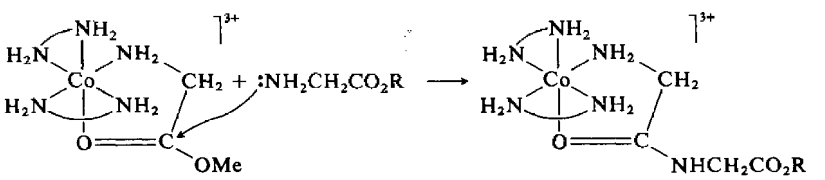
It was subsequently found that treatment of *cis*-$[Co(en)_2(GlyOR)Cl]^{2+}$ with $AgClO_4$ in acetone[138] gave $[Co(en)_2(GlyOR)](ClO_4)_3$ (**30**). This complex can be used for the synthesis of peptide esters.[138] Thus treatment of $[Co(en)_2(GlyOMe)](ClO_4)_3$ with amino acid or peptide esters in anhydrous sulfolane, dimethyl sulfoxide or acetone solution gave the $[Co(en)_2(peptide\text{-}OR)]^{3+}$



(31) (30)

Scheme 3

ion (**32**). Kinetic data for the hydrolysis of $[Co(en)_2(GlyOPr^i)](ClO_4)_3$ have been reported.[139] For the pH-independent attack by water in acidic solution $k = 1.15 \times 10^{-3}\ s^{-1}$ at 25 °C, and evidence for base hydrolysis at pH 8.5 was obtained. The pH-independent rate constant was identical to that obtained in the second step of the Hg^{II}-promoted hydrolysis of *cis*-$[Co(en)_2Cl(GlyOPr^i)]^{2+}$. These kinetic results thus confirm that a chelated ester intermediate is formed following the Hg^{II}-promoted removal of halide ion from the chloropentamine complex (**29**). Isotope studies using ^{18}O establish that hydrolysis of the chelated ester occurs without rupture of the chelate ring. A similar chelated ester intermediate is generated following HOCl oxidation of the coordinated bromide in $[Co(en)_2Br(GlyOR)]^{2+}$ but some of the aqua complex $[Co(en)_2(H_2O)(GlyOR)]^{3+}$ is also produced in this reaction.



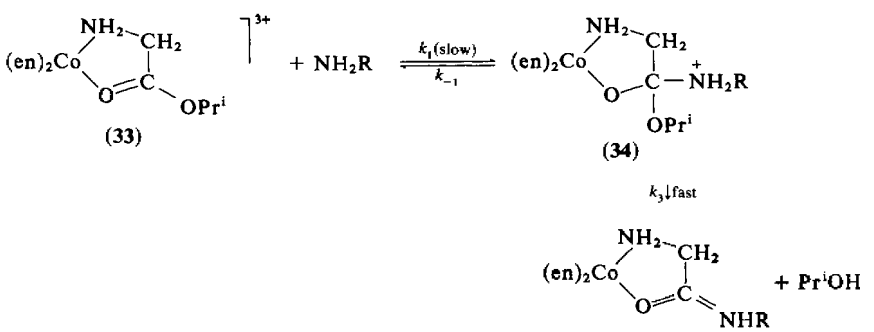
(**32**)

The rates of hydrolysis of chelated ester species are independent of pH in the range 0–4.[137,139,140] This result is expected as coordination to Co^{III} prevents protonation of the carbonyl oxygen and consequent acid hydrolysis. Base hydrolysis of the chelated isopropylglycine in $[Co(en)_2(GlyOPr^i)]^{3+}$ ($k_{OH} = 1.5 \times 10^6\ M^{-1}\ s^{-1}$ at 25 °C) is about 10^6-fold faster than hydrolysis of the free unprotonated ester.[140] The rate enhancement is entirely due to a more positive $\Delta S^{\ddagger}$ in the chelated ester species.[140,141]

Detailed kinetic investigations have subsequently been made[142] of the hydrolysis and aminolysis of $[Co(en)_2(GlyOPr^i)]^{3+}$ (Scheme 4). It was found that over the pH range 0–7 in buffer solutions $k_{obs} = k_{H_2O} + k_{OH}[OH^-] + k_B[B]$, where B is the buffer base. Both oxygen bases (*e.g.* acetate) and nitrogen bases acted as nucleophiles rather than as general bases; the nitrogen nucleophiles formed stable chelated amides or peptides. Somewhat surprisingly it was concluded that k_1 is rate determining in all such substitution reactions even though (**33**) is highly activated towards nucleophilic attack and contains a poor leaving group.

The reaction of (**33**) with glycine ethyl ester in DMSO solution has also been studied kinetically and the tetrahedral intermediate (**34**) detected spectrophotometrically.[143]

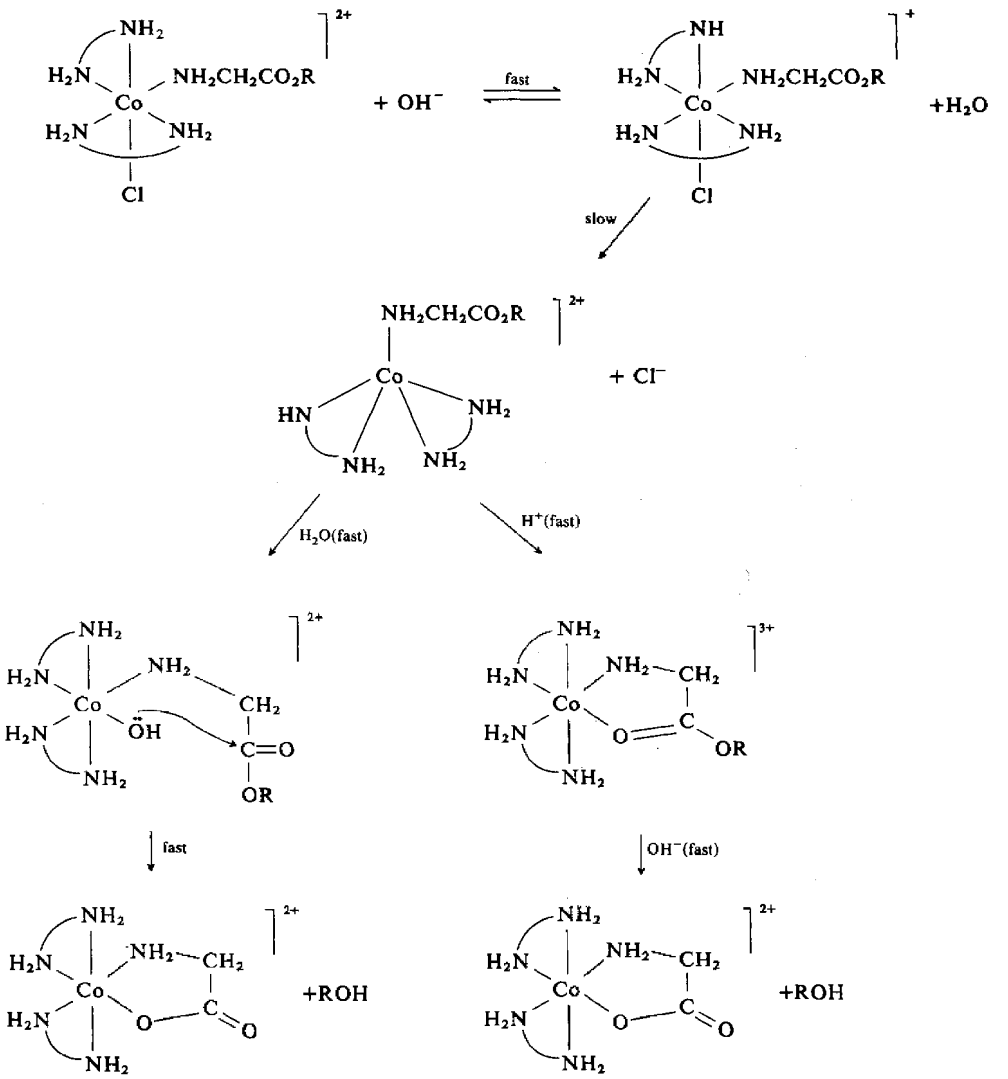
It has been suggested[144] that high concentrations of ClO_4^- alter the mechanism of the Hg^{II}-promoted hydrolysis of *cis*-$[Co(en)_2X(GlyOEt)]^{2+}$ (X = Cl, Br), with high ClO_4^- concentrations



Scheme 4

(>4 M) giving a significant amount of $[Co(en)_2(H_2O)(GlyOEt)]^{3+}$ which only slowly ($t_{\frac{1}{2}} \approx 23$ min) reverted to the chelated ester intermediate with loss of bound water. As such high ClO_4^- concentrations would be expected to significantly reduce the free water concentration these observations seem questionable. Buckingham and Wein[145] have subsequently shown that ClO_4^- does not alter the mechanism, but alters the rate, and in the presence of Hg^{II} the reaction proceeds exclusively *via* the chelated ester intermediate.

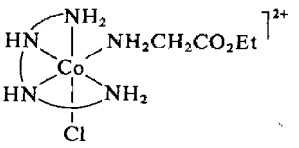
Studies of the base hydrolysis of *cis*-$[Co(en)_2(GlyOR)X]^{2+}$ ions led to interesting developments. Base hydrolysis of halopentamine complexes of cobalt(III) occurs by an S_N1CB mechanism leading to a five-coordinate intermediate. In the N-bonded ester complexes of the $[Co(en)_2(GlyOR)Cl]^{2+}$ type, the ester carbonyl group and solvent water can compete for the vacant site in the five-coordinate intermediate (Scheme 5) giving rise to the chelated glycine ester species and the hydroxypentamine respectively.



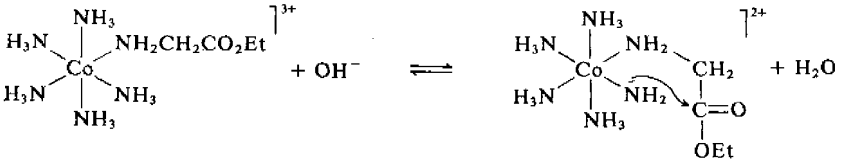
Scheme 5 Pathways to $[Co(en)_2Gly]^{2+}$

Tracer studies[139] using ^{18}O have established that the two main pathways to the chelated glycine complex (which is not the sole product) are (a) internal nucleophilic attack by bound hydroxide ion on the N-coordinated ester and (b) attack of 'external' hydroxide on the chelated ester.

Further investigations[146] have dealt with the Hg^{II}-promoted hydrolysis and base hydrolysis of the β_2-$[Co(trien)Cl(GlyOEt)]^{2+}$ in (**35**). In this case, base hydrolysis gives only chelated glycine products, and ^{18}O tracer studies confirm that some 84% of the β_2-$[Co(trien)Gly]^{2+}$ arises *via* the chelated ester and the remainder by intramolecular nucleophilic attack by coordinated hydroxide.



(35)



(36)

An interesting example of intramolecular attack is seen[147] in the base hydrolysis of $[Co(NH_3)_5NH_2CH_2CO_2R]^{3+}$. Base hydrolysis in the pH range 9–14 gives both $[Co(NH_3)_5(NH_2CH_2CO_2^-)]^{2+}$, containing the monodentate glycinate anion, and $[Co(NH_3)_4(NH_2CH_2CONH)]^{2+}$, with glycinamide bonded *via* both nitrogen atoms. The formation of chelated glycinamide can be rationalized in terms of intramolecular attack within the amido complex (**36**). Similar intramolecular effects are seen in the base hydrolysis of $[Co(en)_2Br(NH_2CH_2Br)]^{2+}$ which leads to N-coordinated aziridines.[148]

Intramolecular effects are only observed with N-coordinated esters of glycine and β-alanine which can give rise to five- and six-membered chelate rings. Base hydrolysis of *cis*-$[CoCl(en)_2(NH_2(CH_2)_5CO_2Me)]^{2+}$[149] and *cis*-$[CoCl(en)_2(NH_2(CH_2)_3CO_2Me)]^{2+}$[150] has been studied. For the first complex, initial chloride hydrolysis is followed by a slower base hydrolysis of the pendant ester function to give the hydroxypentamine, and similar results were obtained with the second complex. Base hydrolysis of the N-coordinated $NH_2(CH_2)_3CO_2Me$ is only *ca.* seven times faster than for $NH_2(CH_2)_3CO_2Me$. Coordination to cobalt(III) *via* the nitrogen has somewhat similar effects to protonation of the amino group.

Base hydrolysis of *cis*-$[Co(en)_2X(NH_2CH_2CH_2OCOMe)]^{2+}$ (X = Cl or Br) in which the ester of an amino-alcohol is employed as the ligand has also been studied.[151] A two-step hydrolysis is observed, the first involving Cl^- or Br^- loss and the second ester hydrolysis. It is noteworthy that N-coordination to cobalt prevents the rapid base-catalyzed isomerization of 2-aminoethyl acetate to 2-acetylaminoethanol.

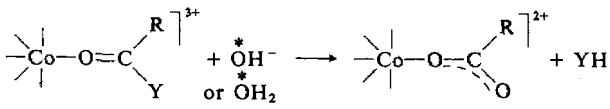
The various pathways by which esters, amides and peptides can undergo hydrolysis can be summarized as shown in Scheme 6.[152] Reaction 1 (the 'metal carbonyl' mechanism) leads to rate enhancements of 10^4–10^6 for all substrates independent of the leaving group Y. The rate enhancement observed in reaction 1 is due solely to a more favourable entropy term, *i.e.* a more positive $\Delta S^{\ddagger}$ for the promoted reaction. Reaction 2 is only effective with more reactive species (CO_2, anhydrides, aldehydes and esters with good leaving groups such as 2,4-dinitrophenyl acetate[153] and 4-nitrophenyl acetate[153,154]). As a result the hydrolysis of alkyl esters of amino acids, amino acid amides and simple peptides has not been observed in a bimolecular 'metal hydroxide' process. Both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ contribute to the rate acceleration in reaction 2. Reaction 1 also leads to nucleophilic attack by nucleophiles other than OH^- (*e.g.* NH_2R, ROH, H_2O) and general acid or general base catalysis can occur.[138,140,142] Only hydrolysis is observed with metal hydroxides and general acid or general base catalysis has not been observed.[155]

Reaction 3, the intramolecular counterpart of reaction 2, has been observed for amino acid esters,[156] amides[157] and nitriles,[158] where five- and six-membered chelate rings can be formed. In the case of the aminoacetonitrile complex (**37**) a rate enhancement of *ca.* 10^{11} occurs at pH 7, and this may be compared with an acceleration of *ca.* 10^6 for the reaction 1 analogue.[159] For reaction 3, $\Delta H^{\ddagger}$ values become of considerable significance.

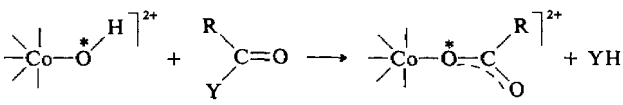
In the case of amino acid ester and amide complexes, the intramolecular hydrolysis reaction was not observed directly, but was deduced from the results of ^{18}O tracer studies. However, recently the *cis*-hydroxo and *cis*-aqua complexes derived from the bis(ethylenediamine)cobalt(III) system, containing glycinamide, glycylglycine and isopropylglycylglycinate, have been isolated and their subsequent cyclization studied over the pH range 0–14.[160,161]

Other related studies have dealt with the base hydrolysis[162] of *cis*-$[Co(en)_2X(GlyO)]^+$ ions (X = Cl, Br) and oxygen exchange and glycinato ring opening in $[Co(en)_2(GlyO)]^{2+}$.[16]

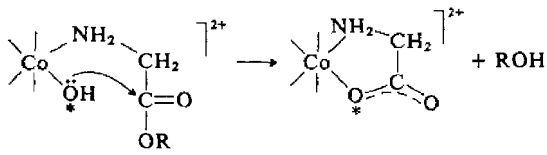
Reaction 1



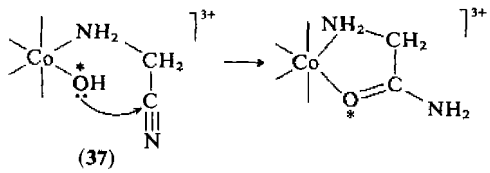
Reaction 2



Reaction 3



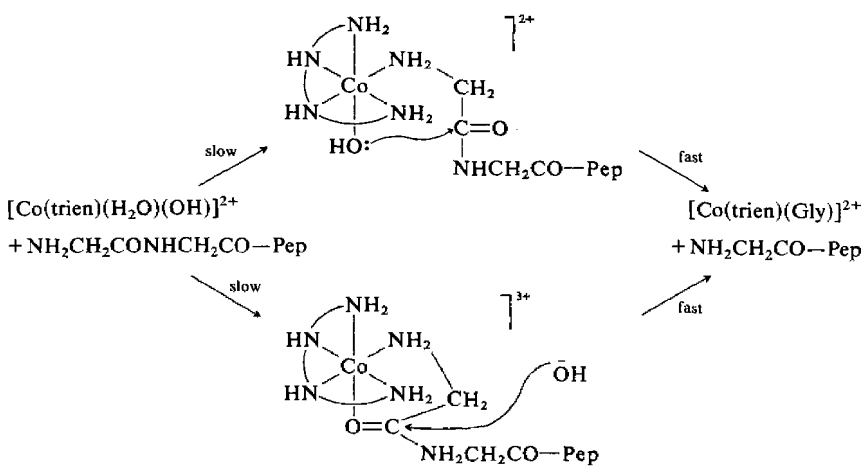
Scheme 6



(37)

61.4.2.2.2 Peptide and amide hydrolysis

A number of complexes of the general type $(CoN_4(OH)(OH_2)]^{2+}$ (N_4 = a system of four nitrogen donors) stoichiometrically cleave the N-terminal amino acid from di-or tri-peptides. Reactions have been described for $N_4 = en_2$,[164–165] trien[166,167] and tren.[168,186] In the case of trien complexes, the proposed mechanism for peptide hydrolysis is shown in Scheme 7. Hydrolysis can occur by two pathways: (a) attack by external hydroxide on the O-bonded chelated peptide, and (b) intramolecular attack of coordinated hydroxide on the N-bonded peptide.



Scheme 7 Proposed mechanisms for peptide hydrolysis

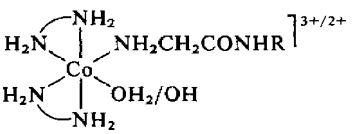
A variety of N-O-chelated glycine amide and peptide complexes of the type $[CoN_4(GlyNR^1R^2)]^{3+}$ have been prepared and their rates of base hydrolysis studied.[169] The kinetics are consistent with Scheme 8. Attack of solvent hydroxide occurs at the carbonyl carbon of the chelated amide or peptide. Amide deprotonation gives an unreactive complex. Rate constants k_{OH} are summarized in Table 16. Direct activation of the carbonyl group by cobalt(III) leads to rate accelerations of *ca.* 10^4-10^6-fold. More recent investigations[160,161] have dealt with

Table 16 Rate Constants for the Base Hydrolysis of Ester, Amide and Peptide Bonds in Various Cobalt(III) Complexes (25 °C, $I = 1.0$ M)[a]

Complex	k_{OH} ($M^{-1} s^{-1}$)
$[Co(en)_2(GlyOPr)]^{3+}$	1.5×10^6
$[Co(en)_2(GlyNH_2)]^{3+}$	25
$[Co(en)_2(GlyNHMe)]^{3+}$	1.6
$[Co(en)_2(GlyNMe_2]^{3+}$	1.1
$[Co(en)_2(GlyGlyO)]^{2+}$	2.6
β_2-$[Co(trien)(GlyNHMe)]^{3+}$	2
β_2-$[Co(trien)(GlyGlyOMe)]^{3+}$	5
β_2-$[Co(trien)(GlyGlyOMe)]^{3+}$	3
β_2-$[Co(trien)(GlyGlyO)]^{2+}$	3

[a] Data from D. A. Buckingham, C. E. Davis, D. M. Foster and A. M. Sargeson, *J. Am. Chem. Soc.*, 1970, **92**, 5571.

intramolecular hydrolysis of glycinamide and glycine dipeptides coordinated to cobalt(III). The intramolecular addition of cobalt(III)-bound H_2O and OH^- to glycinamide, glycylglycine isopropyl ester and glycylglycine in complexes of type (**38**) has been investigated in detail.[161] The aqua dipeptide complex hydrolyzes 10^{11} times more rapidly than the free dipeptide (pH 5) and a factor of 10^7 is involved for the hydroxo dipeptide complex at pH 8. Coordinated water is more reactive than coordinated hydroxide mainly due to a more positive value of $\Delta S^{\ddagger}$. An extensive review of this topic is available.[23] Also see reference 21.



(**38**) R = H, $CH_2CO_2Pr^i$, $CH_2CO_2^-$

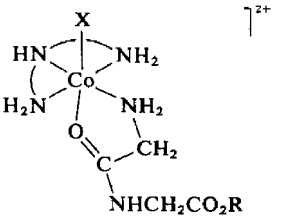
Some of the difficulties in the use of β-$[Co(trien)(OH)(OH_2)]^{2+}$ for the sequential analysis of peptides have been discussed.[170–174] An investigation[173] of the relative effectiveness of the complexes *cis*-β-$[Co(trien)(OH)(OH_2)]^{2+}$, *cis*-$\alpha$-$[Co(trien)(OH)(OH_2)]^{2+}$, $[Co(en)_2(OH)(OH_2)]^{2+}$, *cis*-$[Co(tren)(OH)(OH_2)]$ and $[Co(NH_3)_4(OH)(OH_2)^{2+}$ in the hydrolysis of glycyl dipeptides and dipeptide esters has shown that the *cis*-β-$[Co(trien)(OH)(OH_2)]^{2+}$ species is at least 50 times more effective than any of the other complexes.

The $[Co(edda)(OH)(OH_2)]$ ion has been reported[175] to be as effective as *cis*-β-$[Co(trien)(OH)(OH_2)]^{2+}$ (edda = ethylenediaminediacetate) in the hydrolysis of L-Ala-L-Phe, and a variety of other ligand systems have been evaluated.[176]

Gillard and Phipps[177] established that $[Co(dien)X_3]$ complexes reacted with triglycine to give $[Co(dien)(GlyGly)]^+$ and free glycine. In this case, the two N-terminal amino acids can be removed in a single step. Wu and Busch[178] subsequently described the preparation of a number of complexes of the type $[CoX(dien)(GlyGlyOR)]^{2+}$ and $[CoX(dien)(GlyO)]^{2+}$ (X = Cl, NO_2). Peptide bond formation (Section 61.4.2.2.4) was shown to occur using the three-site moiety $[Co(dien)]^{3+}$. Girgis and Legg[179] established that $[Co(dien)(OH)(OH_2)]$ cleaves the peptide bond of α-L-aspartylglycine, and also studied the $[Co(trien)(OH)(OH_2)]^{2+}$-promoted hydrolysis of the diethyl ester of L-aspartic acid and dipeptides containing aspartic acid, glutamic acid and methionine.

The $[Co(dien)(GlyGlyOR)X]^{2+}$ complexes prepared by Wu and Busch[178] have the configuration (**39**), in which the dien ligand adopts a *mer* configuration and the ligand X lies *trans* to oxygen. A series of *trans*-(O,X)-$[CoX(dien)(AA)]^+$ complexes (AA^- = amino acid anion, X = Cl, NO_2, CN) have been prepared.

Complexes such as (**39**) are likely intermediates in the reaction of $[Co(dien)(OH)(OH_2)_2]^{2+}$ with dipeptides.[177,181] Hay and Piplani[182] have studied the kinetics of base hydrolysis of a variety of complexes of type (**39**) and have determined values of k_{OH} for hydrolysis of the peptide bond and the NO_2 and Cl ligands (Table 17). The rate constant k_{OH} for peptide bond hydrolysis falls within the range 0.7 to 7 $M^{-1} s^{-1}$ and is some 10^4 to 10^5 times greater than that for the uncomplexed peptide.



(39)

Table 17 Base Hydrolysis of the Peptide Bond and the NO_2 and Cl Ligands in Co(dien) Complexes at $I = 0.1$ M and 25 °C[a]

Initial complex	$k_{OH}^{peptide}$ ($M^{-1}\,s^{-1}$)	$k_{OH}^{NO_2}$ ($M^{-1}\,s^{-1}$)	k_{OH}^{Cl} ($M^{-1}\,s^{-1}$)
$[Co(dien)(GlyGlyO)NO_2]^+$	0.88		
$[Co(dien)(GlyGlyGlyO)NO_2]^+$	0.67		
$[Co(dien)(GlyGlyOEt)NO_2]^{2+}$	0.68	2.5×10^{-2}	
$[CoCl(dien)(GlyGlyOEt)]^{2+}$	7.0		1.1×10^{6}
$[CoCl(dien)(GlyO)]^+$	—		1.3×10^{4}
$[CoCl(dien)(GlyNH_2)]^{2+}$	—		5.85×10^{5}
$[Co(dien)(GlyO)NO_2]^+$	—	2.45×10^{-2}	

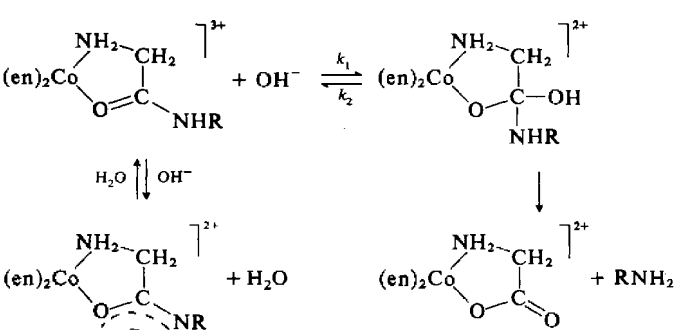
[a] For base hydrolysis of glycylglycine, $k_{OH} \approx 4\times10^{-5}\ M^{-1}\,s^{-1}$ at 26 °C. Data from R. W. Hay and D. P. Piplani, *Kem. Kozl.* 1977, **48**, 47. For additional data see R. W. Hay, V. M. C. Reid and D. P. Piplani, *Transition Met. Chem.*, 1986, **11**, 302.

The synthesis and base hydrolysis of $[M(NH_3)_5DMF]^{3+}$ containing O-bonded DMF (M = Co^{III},[183] Rh^{III} [184] and Ir^{III} [184]) has been studied in detail. Two reaction pathways are observed with the cobalt(III) complex. The major pathway corresponds to hydroxide ion attack at the carbonyl centre giving $[Co(NH_3)_5OOCH]^{2+}$ and $HNMe_2$. The minor path leads to $[Co(NH_3)_5OH]^{2+}$ and DMF, and is the dissociative conjugate base process. Amide cleavage is accelerated at least 10^4 times due solely to a more favourable entropy term. Hydrolysis of the Rh^{III} and Ir^{III} complexes corresponds to equation (17). In this case there is no evidence for any ligand loss by a conjugate base mechanism to give free DMF and the pentaamminehydroxo species. The kinetics fit the rate equation $k_{obs} = k_1[OH] + k_2[OH]^2$. For the k_1 pathway the rate enhancement (*ca.* 10^6-fold) occurs due to a more positive value of $\Delta S^{\ddagger}$. Values of $\Delta H^{\ddagger}$ are essentially the same as for the free ligand.

$$[(NH_3)_5MOCHNMe_2]^{3+} + OH^- \rightarrow [(NH_3)_5MOOCH]^{2+} + HNMe_2 \qquad (17)$$

The work described above suggests that carbonyl-bonded amides and peptides when coordinated to Co^{III}, Rh^{III} and Ir^{III} will undergo base hydrolysis *ca.* 10^6 times faster than the free ligand, the rate acceleration arising primarily from a more positive value of $\Delta S^{\ddagger}$. At high pH, amide deprotonation occurs (Scheme 8) leading to catalytically inactive complexes. Much higher rate accelerations can be obtained if intramolecular attack by coordinated water or hydroxide ion can take place (*ca.* 10^7–10^{11}-fold).

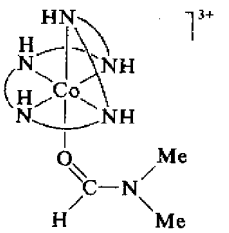
Recent work[160] also clarifies a previous report on the hydrolysis of *cis*-$[Co(en)_2Br(GlyNH_2)]^{2+}$. In the initial study[157] it was concluded that the hydroxo glycinamide ion reacted rapidly under the conditions of base hydrolysis and the subsequent process observed spectrophotometrically



Scheme 8 Base hydrolysis of carbonyl-bonded amides and peptides

was hydrolysis of the chelated amide. Chan and Chan[185] had earlier reported that a relatively stable hydroxo species was first formed, and this conclusion has now been confirmed. Base hydrolysis of *cis*-$[Co(en)_2Br(GlyNH_2)]^{2+}$ gives considerable amounts of the hydroxo amide complex $[Co(en)_2(OH)(GlyNH_2)]^{2+}$ in addition to the chelated amide.

Base hydrolysis of O-coordinated *N,N*-dimethylformamide in the complex $[Co([15]aneN_5)DMF]^{3+}$ (**40**)[187] is accelerated some 327-fold compared with the free ligand. The effect is considerably less marked in the macrocyclic complex when comparisons are made with the $[Co(NH_3)_5(DMF)]^{2+}$ complex (rate acceleration *ca.* 10^4). The Lewis acidity of Co^{III} is presumably reduced by the stronger σ-donors of the macrocyclic ligand.

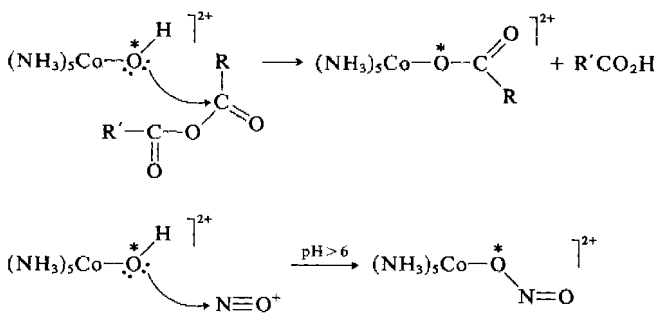


(**40**)

61.4.2.2.3 Cobalt hydroxide-promoted hydrolysis and lactonization

Hydroxide ion coordinated to cobalt(III) has been observed to function as a nucleophile in both intermolecular and intramolecular reactions. The possibility that coordinated hydroxide is directly involved in the catalytic action of some metalloenzymes such as carbonic anhydrase has prompted a number of investigations of metal hydroxide reactivity towards organic substrates. Much of this chemistry has been reported and reviewed.[21,23]

Reactions of the $[Co(NH_3)_5OH]^{2+}$ or $[Co(NH_3)_5OH_2]^{3+}$ ion with a range of species including NO^+,[188] NCO^-,[189] CO_2,[190] SO_2,[191] carboxylic acid esters and anhydrides,[23,192,200,201] acetylacetone,[193] $HSeO_3^-$,[194] WO_4^{2-},[195] MoO_4^{2-},[196] $H_2AsO_4^-/HAsO_4^{2-}$[197] and HIO_3[198] take place at rates orders of magnitude faster than the rates of normal substitution or water exchange reactions of the cobalt(III) complexes. In those cases where ^{18}O tracer experiments have been carried out, it has been shown that the donor oxygen of the product is derived from the coordinated water or hydroxide. The products are formed by reactions involving coordinated OH^- acting as a nucleophile, rather than by substitution at the cobalt(III) centre (Scheme 9). The nucleophilicity of a series of structurally related bases is generally related to the pK_a of their conjugate acids (the Brönsted relationship). As metal ions are normally weaker Lewis acids than H^+, their aqua complexes have pK_a values intermediate between those of H_3O^+ (−1.74) and H_2O (15.74). On this basis the nucleophilicity of $MOH^{(n-1)+}$ species would be expected to be intermediate between that of H_2O and OH^-.



Scheme 9

The $[Co(NH_3)_5OH]^{2+}$-promoted hydrolysis (and that promoted by other exchange-labile and non-labile metal hydroxide species) of 2,4-dinitrophenyl acetate and 4-nitrophenyl acetate has been studied in some detail.[199] Kinetic studies (25 °C, $I = 1.0$ M) show that these reactions follow shallow Brönsted slopes ($\beta = 0.33$ and 0.40) for the two substrates which extend over a range of 10^{10} in nucleophile basicity. A correlation is reported which allows the prediction of reaction

rates between $[Co(NH_3)_5OH]^{2+}$ and other activated charge neutral carbonyl substrates, such as CO_2 and propionic anhydride.

The kinetics of acylation of a series of $MOH^{(n-1)+}$ complexes by propionic anhydride and carboxylic esters containing good leaving groups have also been examined in detail.[23,200] The inert hydroxo complexes used were $[Co(NH_3)_5(OH)]^{2+}$, $[Cr(NH_3)_5(OH)]^{2+}$, $[Ru(NH_3)_5(OH)]^{2+}$, $[Ir(NH_3)_5(OH)]^{2+}$, $(Cr(H_2O)_5(OH)]^{2+}$, *trans*-$[Co(NH_3)_4(NO_2)(OH)]^{+}$ and $[Co(CN)_5(OH)]^{3-}$. The pK_a of the corresponding aqua complex varied between *ca.* 4 for $[Cr(H_2O)_6]^{3+}$ and *ca.* 10 for $[Co(CN)_5(OH_2)]^{2-}$ while the overall charge varied between 2+ and 3−. The rate expression for these reactions is rate $= k_{MOH}[MOH][substrate]$ at high pH and rate $= k_{MOH_2}[MOH_2][substrate]$ at low pH. The ratio k_{MOH}/k_{MOH_2} was always greater than 10^3 confirming the higher nucleophilicity of the hydroxo complex.

For the reaction of $MOH^{(n-1)+}$ with propionic anhydride,[200] the Brönsted plot of log k_{MOH} *versus* the pK_a of MOH_2^{n+} follows a smooth curve if the values for H_2O and OH^- are included (Figure 4). However, if the line is drawn to exclude the k_{H_2O} value, a Brönsted β of *ca.* 0.25 is obtained. Although k_{MOH} for $[Co(NH_3)_5OH]^{2+}$ (3 M^{-1} s^{-1}) is some 10^3-fold less than k_{OH}, this reaction will compete favourably at neutral pH with base hydrolysis. At pH 7 where the cobalt(III) complex exists almost completely as the MOH^{2+} species the observed first order rate constant for nucleophilic attack by OH^- would be *ca.* 10^{-4} s^{-1}. A 1 M solution of $[Co(NH_3)_5OH]^{2+}$ would give a value of $k_{obs} \approx 2.5$ s^{-1}, a rate acceleration of $>10^4$-fold. Since the 'effective' concentration of a nucleophile in the intramolecular reaction could be *ca.* 10^2 M, rate accelerations of 10^6 are possible. The role of the metal ion in such reactions is to provide an effective concentration of an efficient nucleophile at low pH.

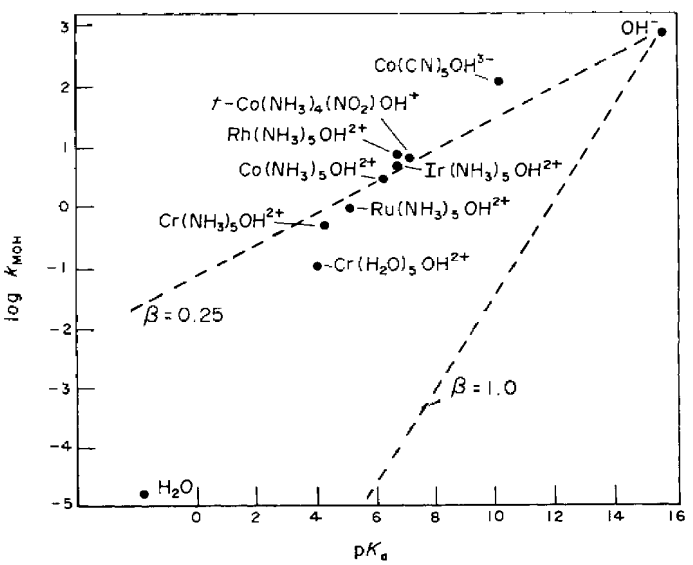
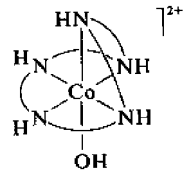


Figure 4 Plot of log k_{MOH} *versus* pK_a (of MOH_2^{n+}) for the reaction of various metal hydroxide complexes with propionic anhydride at 25 °C and $I = 1.0$ M ($NaClO_4$) (reproduced with permission from 'Biological Aspects of Inorganic Chemistry', Wiley, New York, 1966)

The cleavage of 4-nitrophenyl acetate by $[Co(NH_3)_5OH]^{2+}$ and $[Co(NH_3)_5Im]^{2+}$ (Im = N-deprotonated imidazole) has been studied in water and DMSO solvents.[192] All the reactions are exclusively nucleophilic as demonstrated by the detection of the acetylated products $[(NH_3)_5CoO_2CMe]^{2+}$ and $[(NH_3)_5CoImCoMe]^{3+}$. Typical kinetic data are summarized in Table 18. The large difference in the reactivity of the two complexes towards 4-nitrophenyl acetate is closely paralleled by their differences in basicity. In Me_2SO the complexes have a similar reactivity towards the ester ($k_{MIm} = 30$ M^{-1} s^{-1}, $k_{MOH} = 0.72$ M^{-1} s^{-1} at 25 °C), and this increase is largely due to the marked increase in the basicity of $[Co(NH_3)_5OH]^{2+}$ relative to that of $[Co(NH_3)_5Im]^{2+}$ in the dipolar aprotic solvent.

It should be remembered that no single value of the Brönsted coefficient β describes the relationship between the basicity of oxygen and other anionic nucleophiles and their nucleophilicity towards esters over a large variation in the structure of the nucleophile. However, the general conclusion can be drawn that oxygen nucleophiles on metal centres will have a nucleophilicity which broadly equates with their basicity.

The hydrolysis of 1-acetylimidazole[202] in the presence of the exchange-inert metal complexes $[Co(NH_3)_5OH]^{2+}$, $[Cr(OH_2)_5OH]^{2+}$ and $[Cr(NH_3)_5OH]^{2+}$ is also of interest. The processes appear to be predominantly nucleophilic in character, as shown by the isolation of a 93% yield of $[Co(NH_3)_5(OCOMe)]^{2+}$ in the reaction of $[Co(NH_3)_5OH]^{2+}$ with the amide. There is little or no contribution from general base catalysis and this appears to be a feature of MOH^{n+} reactions of this type.



(41)

The hydrolysis of 4-nitrophenyl acetate in the presence of the macrocyclic complex $[Co([15)aneN_5)OH)]^{2+}$ (**41**) is somewhat faster[201] than the $[Co(NH_3)_5OH]^{2+}$-promoted hydrolysis (Table 18).

Table 18 Rate Constants for the Hydrolysis of 4-Nitrophenyl Acetate by Various Nucleophiles in Water Solvent[a]

	k ($M^{-1}s^{-1}$, 25 °C)	pK_a[b]
OH^-	16.5	15.5
Imidazole	0.58	14
$[(NH_3)_5CoIm]^{2+}$	9	10.02
Carbonic anhydrase	460	7.5
$[Co([15]aneN_5)OH]^{2+}$	9.3×10^{-3}	6.3
$[(NH_3)_5CoOH]^{2+}$	1.52×10^{-3}	6.4

[a] Data from J. MacB. Harrowfield, V. Norris and A. M. Sargeson, *J. Am. Chem. Soc.*, 1976, **98**, 7282 and R. W. Hay and R. Bembi, *Inorg. Chem. Acta*, 1982, **64**, L179.
[b] pK_a of the conjugate acid.

61.4.2.2.4 Peptide bond formation

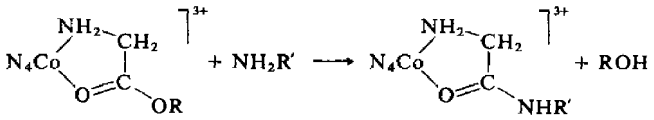
The rapid condensation of glycine ethyl ester to form glycylglycine ethyl ester using the $[Co(trien)]^{3+}$ moiety as an N-terminal protecting group and an activating reagent was first established in 1967.[203] The rapid and quantitative formation of chelated peptide esters using the isolated intermediate $[Co(en)_2(GlyOMe)](ClO_4)_3$ has been shown to occur.[138] Treatment of $[Co(en)_2(GlyOMe)](ClO_4)_3$ with amino acid or peptide esters in anhydrous sulfolane, DMSO or acetone solutions results in the rapid formation of the $[Co(en)_2(peptide\text{-}OR)]^{3+}$ ion. The reactions are rapid at 20 °C, being complete in minutes.

Peptide bond formation in the coordination sphere of cobalt(III) is also observed[204] in the reaction of *cis*-$[Co(trien)Cl_2]Cl$ with glycine esters to give *cis*-β-$[Co(trien)(GlyGlyOR)]^{3+}$. Kinetic and product analysis data for the reaction of $[Co(en)_2(GlyOPr^i)](ClO_4)_3$ with H_2O, HO^-, NH_2CH_2CN and $MeCO_2^-$ have been reported.[205] For base hydrolysis $k_{OH} = 0.8\times10^6\ M^{-1}\ s^{-1}$ and for water attack $k_{H_2O} = 1.89\times10^{-5}\ M^{-1}\ s^{-1}$ at 25 °C and $I = 1.0$ M. The preparation of $[Co(en)_2(Gly\text{-}OPr^i)](ClO_4)_3$ has been described.[143] Attack of a glycine ester at the carbonyl centre occurs with $k = 14\ M^{-1}\ s^{-1}$ at 25 °C. A second reaction is observed attributed to general acid-catalyzed removal of isopropanol from the conjugate base of the tetrahedral intermediate.

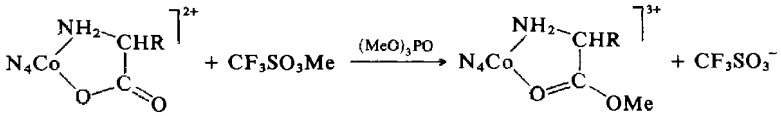
The structure of the complex *cis*-$[Co(trien)(GlyGlyOEt)](ClO_4)_3\cdot H_2O$ has been determined by X-ray diffraction.[206] The peptide ester is coordinated *via* the terminal amino group and the carbonyl oxygen of the same amino acid residue.

The reaction of $[Co(dien)X_3]$ ($X = Cl$, NO_2) with glycine esters and glycylglycine esters gives $[Co(dien)(GlyGlyOR)X]^{2+}$ and $[Co(dien)(GlyGlyGlyOR)]^{2+}$ respectively.[178]

The rapid aminolysis of cobalt(III)-chelated glycine esters in aprotic solvents (Scheme 10; $N_4 = (en)_2$ or trien, R = Me, Et, R′ = H, CHR″CO_2Et) could be of value in peptide synthesis. The cobalt atom acts as both an N-protecting and an activating group. The synthesis of the chelated amino acid esters has presented some difficulties.[207] A recent paper[208] describes the use of methyl trifluoromethanesulfonate for the alkylation of chelated amino acids using dry trimethyl phosphate



Scheme 10

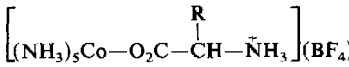


Scheme 11

as solvent (Scheme 11). The cobalt(III) amino acid methyl esters are readily isolated as orange powders following trituration with Et_2O/MeOH. Some have been recrystallized from MeOH as ClO_4^- or I^- salts. Their coupling is rapid in dry DMSO, acetonitrile or methanol. The $[Co(en)_2]^{3+}$ and $[Co(trien)]^{3+}$ moieties are chiral and some specificity is induced when optically active cobalt(III) units are employed. Kinetic studies in acetonitrile solvent show that coupling to Δ- and Λ-$[Co(en)_2(AA\text{-}OMe)](CF_3SO_3)_3$ follows overall second order kinetics with specific rate ratios k_Λ/k_Δ of 2.7, 1.0, 2.0 and 1.5 for the combinations CoAA-OMe : AA-OEt = Ala : Phe, Phe : Phe, Val : Phe and Ala : Val. By choosing the appropriate cobalt(III) chirality some control can be exercised in avoiding couplings to mutarotated amino acid residues.

The synthesis of tetrapeptides and [leu^5]enkephalin by the cobalt(III) technique has been described.[209]

Pentaamminecobalt(III) has now been shown to be a useful C-terminal protecting group for sequential peptide synthesis.[210] The reaction of complexes of type (**42**) with BOC amino acid active esters or BOC symmetric anhydrides gives $[Co(AA)^1(AA)^2BOC]$. The BOC group is removed with 95% CF_3CO_2H to give $[Co(AA)^1(AA)^2]$ which can be used for sequential peptide synthesis. Alternatively the $(NH_3)_5Co$ group is selectively removed by rapid reduction with $NaBH_4$ or NaHS to give the N-protected peptide fragment $[(AA)^1(AA)^2BOC]$ under very mild conditions. The general procedures are discussed and the preparation of a number of penta- and hexa-peptides by this route is described.

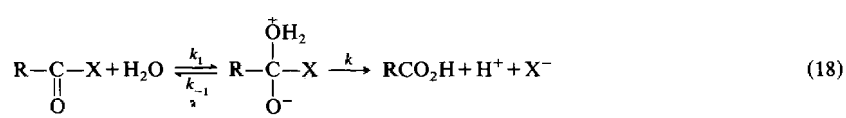


(**42**) = $[Co(AA)_1]$

61.4.3 HYDROLYSIS OF CARBOXYLIC ESTERS AND AMIDES

In addition to the large volume of literature dealing with the metal ion-promoted hydrolysis of α-amino acid esters, amides and peptides a considerable amount of work has been reported on other esters and amides. These developments are considered in the present section.

Esters and amides of carboxylic acids usually undergo hydrolysis by an associative mechanism (equation 18) involving a tetrahedral intermediate (**43**) rather than undergoing solvolysis to give an oxocarbonium ion (equation 19). Metal ion coordination of the carbonyl oxygen can accelerate the process by stabilizing the tetrahedral intermediate and by increasing the susceptibility of the carbonyl oxygen to nucleophilic attack (general acid catalysis). Metal ion coordination of the leaving group X can accelerate the reaction in two ways. First, it can reduce the delocalization of lone pairs from X into the carbonyl group in the ground state, thus making the carbonyl group more susceptible to nucleophilic attack. Second, coordination of X can stabilize it during its departure from the tetrahedral intermediate.



(18)

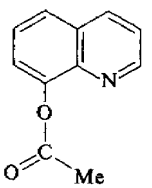
(**43**)



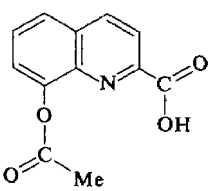
(19)

(X = OR, NR_2, SR)

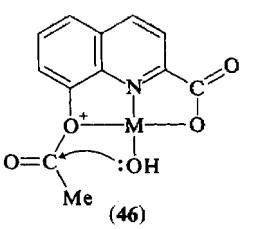
Examples of both types can be seen in the hydrolysis of carboxylic esters of 8-hydroxyquinoline.[211-214] The hydrolysis of 8-acetoxyquinoline (**44**) is promoted by metal ions,[213] but as the formation constants for metal complex formation are rather low, the system is not very amenable to detailed kinetic analysis. The derivative 8-acetoxyquinoline-2-carboxylic acid (**45**) with an additional bonding site complexes strongly to a variety of metal ions and detailed kinetic studies are possible.[214] In the pH range 5–12 the hydrolysis of the stubstrate (HA) follows the rate law, rate $= k_0[A^-] + k_{OH}[A^-][OH^-]$, where A^- is the anion, with $k_0 = 1.67 \times 10^{-4}\ s^{-1}$ and $k_{OH} = 0.84\ M^{-1}\ s^{-1}$ at 25 °C. The 1:1 metal complexes of the ester MA^+ ($M = Zn^{II}$ and Cu^{II}) undergo base hydrolysis *ca.* 2×10^8 times faster than A^-. The metal ion-promoted reactions are considered to involve attack by coordinated hydroxide (**46**), and this intramolecular effect in conjuction with a perturbation of *ca.* 6 pK units in the acidity of the conjugate acid of the leaving group leads to very high rates of hydrolysis, comparable with the reported values of k_{cat} for the hydrolysis of a good ester substrate by the zinc metalloenzyme carboxypeptidase A.



(**44**)

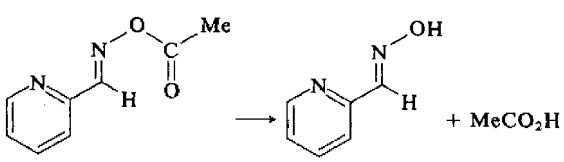


(**45**)

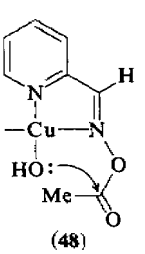


(**46**)

Somewhat similar effects are seen in the copper(II)-promoted hydrolysis of *O*-acetyl-2-pyridinecarboxaldoxime (**47**) (equation 20).[215] In this case, water attack and hydroxide ion attack are accelerated by 1.1×10^4 and 2.2×10^7 times respectively. Detailed analysis indicates that Cu^{II}-bound water or hydroxide reacts with the carbonyl carbon of the ester as shown in (**48**). Promotion includes contributions from increases in the effective nucleophile concentration in addition to an enhancement in the leaving group ability. General base catalysis in the attack of coordinated water is also observed.

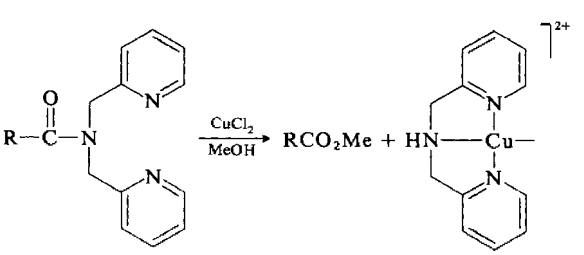


(**47**) (20)



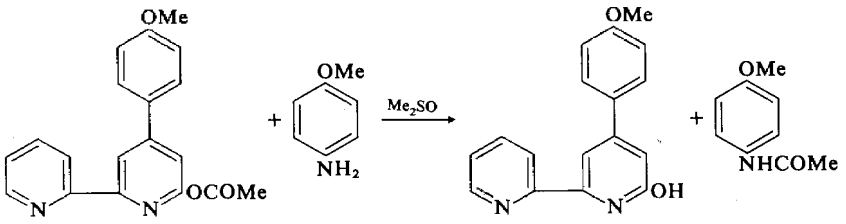
(**48**)

The methanolysis of amides of *N,N*-di(2-picolyl)amine (Scheme 12) also illustrates the leaving group effect.[216] Addition of the *p*-nitrophenyl derivative to a hot solution of $CuCl_2$ in methanol



R = *p*-$NO_2C_6H_4$, Bu^t or MeCH=CH—

Scheme 12



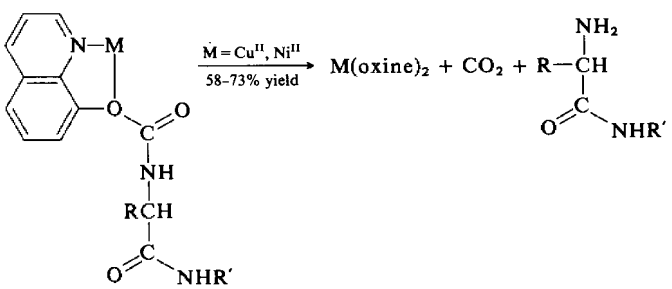
(49)

Scheme 13

results in 'almost instantaneous' formation of methyl *p*-nitrobenzoate and the deep blue copper(II) complex of di(2-picolylamine). Heating the ligand alone in methanol for 24 hours in the absence of copper(II) gave no methyl *p*-nitrobenzoate. In addition, no ester was formed on heating *N,N*-dibenzyl-*p*-nitrobenzamide with $CuCl_2$ in methanol for 24 hours. Chelation of the metal ion by the leaving group leads to a very large increase in the methanolysis rate. Increased hydrolysis rates in aqueous solution were also noted.

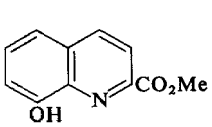
A number of attempts have been made to use reactions of this type for synthetic purposes. The ligand (**49**) can be used as an acylating reagent (Scheme 13). Acylation rates in Me_2SO are greatly increased by the addition of transition metal ions such as Zn^{II}, Co^{II} and Ni^{II}.[217] As a result it is possible to prepare acylating reagents whose reactivity can be 'switched on' by addition of a transition metal ion.

As carboxylic esters of 8-hydroxyquinoline are readily hydrolyzed in the presence of metal ions, it has been possible to develop the carbo(8-quinoloxy) substituent as an amino-protecting group for peptide synthesis (Scheme 14).

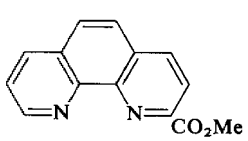


Scheme 14

Metal ions have quite marked effects on the hydrolysis of methyl 8-hydroxyquinoline-2-carboxylate (**50**)[218] and ethyl 1,10-phenanthroline-2-carboxylate (**51**).[219] Base hydrolysis of the 8-hydroxyquinoline derivative (**50**) was studied over the pH range 9.2–12.1 and values of k_{OH} determined for HA and the anion A^-. Formation constants K_{MA^+} were determined at 25 °C for the equilibrium $M^{2+} + A^- \rightleftharpoons MA^+$, as were the rate constants k_{OH} for the base hydrolysis of the MA^+ complexes (Table 19). Quite large rate accelerations are observed (10^3–10^6) when comparisons are made with the base hydrolysis of A^-. The charge carried by the complex does not appear to be a major factor in determining base hydrolysis rates. Thus at 25 °C the complex CuA^+ undergoes base hydrolysis ($k_{OH} = 6.3 \times 10^5\ M^{-1}\ s^{-1}$) at a very similar rate to the corresponding copper(II) complex of ethyl 1,10-phenanthroline-2-carboxylate (**51**) which carries a dipositive charge (k_{OH}) $= 5 \times 10^5\ M^{-1}\ s^{-1}$).[219]



(50)



(51)

Some interesting conclusions can be drawn from the thermodynamic parameters for base hydrolysis of the MA^+ complexes (Table 19). The rate enhancements in the metal ion-promoted reactions arise from more positive values of ΔS^+ and, in general, lower enthalpies of activation. In addition, there is a close correspondence between values of log K_{MA^+} and ΔG^+ (Figure 5). The general trends in ΔH^+ and ΔS^+ in the metal-promoted reactions can be rationalized in terms

Table 19 Rate Constants, Activation Parameters and Formation Constants for the Metal Complexes of Methyl 8-Hydroxyquinoline-2-carboxylate[a]

Complex	K_{MA^+}[b] (M^{-1})	k_{OH}[b] ($M^{-1}s^{-1}$)	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}_{98}$ (J K^{-1} mol^{-1})
HA	—	4.0		
A^-	—	0.485	47.7	−90.8
MnA^+	4.9×10^4	4.9×10^2	47.7	−33.1
ZnA^+	3.8×10^6	2.6×10^3	54.4	2.9
NiA^+	5.6×10^5	1.01×10^4	30.5	−65.3
CoA^+	3.4×10^5	1.12×10^4	38.1	−39.7
CuA^+	$>2\times10^8$	6.3×10^5	33.1	−22.6

[a] Data taken from R. W. Hay and C. R. Clark, *J. Chem. Soc., Dalton Trans.*, 1977, 1866.
[b] Rate constants and formation constants at 25 °C.

of ground state and transition state interactions between the metal ion and the carbonyl group of the ester. Where a strong interaction occurs between the metal ion and the ester function in the ground state of the reaction, as appears to occur in the nickel(II)-promoted reaction, the value of $\Delta H^{\ddagger}$ is significantly lowered due to polarization of the carbonyl group, but $\Delta S^{\ddagger}$ remains quite negative as there is little change in solvation on moving to the transition state. If ground state interactions are weak, but a significant interaction occurs in the transition state, as appears to be the case with Zn^{II}, $\Delta H^{\ddagger}$ remains quite large, but $\Delta S^{\ddagger}$ is significantly lowered as the metal ion is able to "solvate" the developing negative charge on the carbonyl group and desolvation is more extensive.

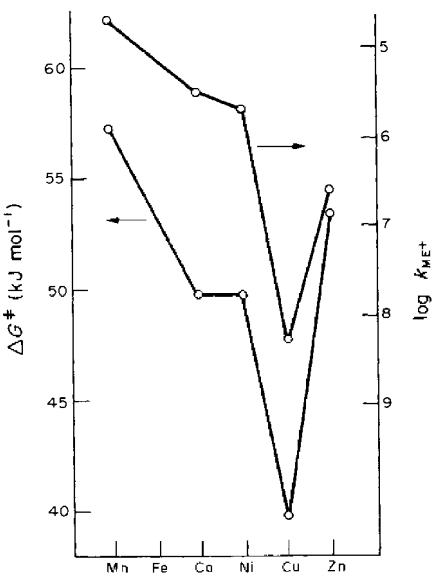
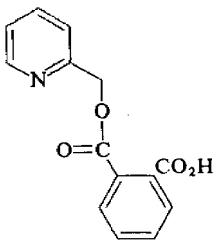


Figure 5 Relation between $\Delta G^{\ddagger}$ for base hydrolysis of $[ME]^+$ and log K_{ME^+}

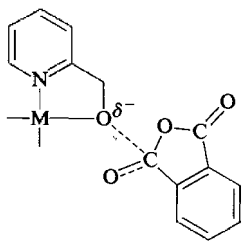
Transition state effects in the divalent metal ion-catalyzed hydrolysis of 2-pyridylmethyl hydrogen phthalate (**52**), an ester with a poor leaving group, have also been studied.[220] Metal ions (Ni^{II}, Co^{II}, Zn^{II}) exert a large catalytic effect, although bonding to the substrate is weak. The metal ion-catalyzed reactions are pH independent (pH 4.7–7.2), indicating carboxylate group participation. Breakdown of the tetrahedral intermediate must be rate determining in such reactions of esters with poor leaving groups.

The metal ions must exert their effect in the transition state by stabilization of the leaving group (**53**). Somewhat similar effects are seen in the metal-promoted hydrolysis of benzaldehyde methyl 8-quinolyl acetals.[221]

The effects of divalent ions (Cu^{II}, Ni^{II}, Co^{II} and Zn^{II}) on the hydrolysis of phthalate, succinate and acetate esters of 2-(hydroxymethyl)picolinic acid (**54**) have been studied to establish if strong bonding of the metal ion to the leaving group oxygen might enhance intramolecular carboxylate attack.[222] With these esters, saturation conditions are observed at low metal ion concentrations

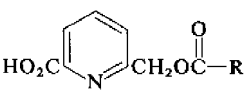


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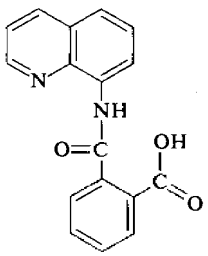


(53)

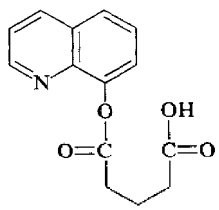
(<0.01 M). Large rate enhancements occur for base hydrolysis of the complexes, ranging from 10^4 with Ni^{II} to 10^6 with Cu^{II}. A pH-independent reaction occurs with the phthalate monoester due to intramolecular nucleophilic attack by the neighbouring carboxylate group leading to rate enhancements of 10^2–10^4. Metal ion-promoted water hydrolysis was also observed with these esters.



(54) R = $C_6H_4CO_2H$-*o*, $(CH_2)_2CO_2H$, Me



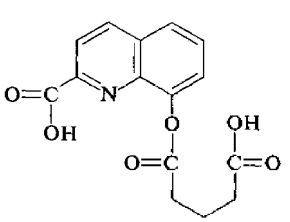
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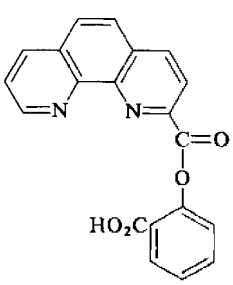
(56)

Fife and Squillacote[223] have studied the effect of metal ions on the hydrolysis of *N*-(8-quinolyl)phthalamic acid (**55**) and 8-quinolyl hydrogen glutarate (**56**) in an attempt to assess their effect on intramolecular nucleophilic carboxyl group participation in amide and ester hydrolysis. The divalent metal ions Cu^{II}, Ni^{II}, Co^{II} and Zn^{II} have little effect on the intramolecular nucleophilic reaction of either the amide or the ester. Above pH 6, the metal ions promote the base hydrolysis of the ester but not the amide. The order of reactivity of the metal complexes is $Zn^{II} > Co^{II} > Ni^{II}$ with rate enhancements ranging from 10^2 to 2×10^4, although full complexation of the substrate was not achieved. The metal-promoted base hydrolysis although leading to quite large rate enhancements cannot compete with intramolecular nucleophilic participation by the carboxylate group below pH 6.

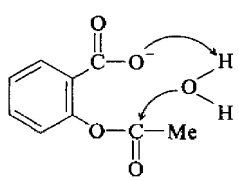
A recent study[224] of the metal ion-promoted hydrolysis of 8-(2-carboxyquinolyl) hydrogen glutarate (**57**) has extended the earlier measurements.[223] Full complexation with Zn^{II} and Cu^{II} was achieved leading to rate enhancements of 4×10^7 for base hydrolysis of the copper(II) complex. Upper limits for rate enhancements due to metal ion catalysis of the carboxylate anion nucleophilic reaction are 10^2 with Ni^{II} and Co^{II} and 10^3 with Cu^{II} and Zn^{II}. These enhancements could arise from a transition state effect in which the leaving group is stabilized. This paper[224] also discusses the effects of metal ions on the intramolecular general base hydrolysis of salicyl phenanthroline-2-carboxylate (**58**). This ester is expected to hydrolyze by an intramolecular general base mechanism analogous to that of aspirin (**59**). In the presence of saturating concentrations of Cu^{II}, Ni^{II}, Co^{II} or Zn^{II} the plot of log k_{obs} *versus* pH is linear with unit slope, indicating a first order dependence on the hydroxide ion concentration. Metal-assisted intramolecular general base catalysis does not compete with base hydrolysis of the metal complex in this system.



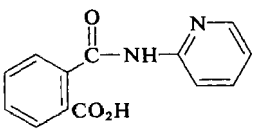
(57)



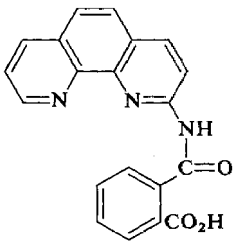
(58)



(59)



(60)



(61)

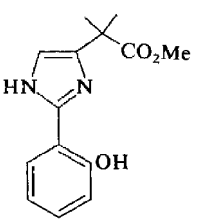
Divalent metal ions inhibit the hydrolysis of *N*-(2-pyridyl)phthalamic acid (**60**) and *N*-(2-phenanthrolyl)phthalamic acid (**61**). In the case of (**61**) the substrate hydrolyzes by a pathway involving intramolecular general acid catalysis, and this pathway is inhibited by metal ions. Deprotonated amide complexes may also be involved leading to catalytically inactive complexes.

Large rate accelerations have been observed in the metal ion-promoted hydrolysis of some lactams and these reactions are considered in Section 61.4.10. Other investigations have dealt with divalent metal ion-catalyzed hydrolysis of *p*-nitrophenyl picolinate in the presence of imidazoles and pyridines having hydroxyl groups in their side chains,[226] the zinc(II)-facilitated hydrolysis of esters of 2-hydroxy acids[227] and the metal ion-promoted hydrolysis of methyl 2-(*N*-acetylhydrazono)propanoate.[228]

61.4.3.1 Reactions Involving Coordinated Hydroxide in Labile Metal Systems

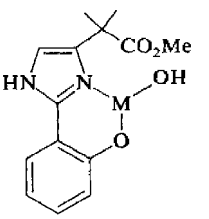
Both intramolecular and intermolecular attack by $M—OH^{n+}$ species are well established for cobalt(III) and other kinetically inert metal centres (Section 61.4.2.2.3). However, reactions of this type are not as well defined with labile metal ions. In copper(II) complexes, the pK_a values for coordinated water ligands usually fall within the range pK_a 6-8. If coordinated hydroxide ion is an important nucleophile in copper(II)-promoted reactions, the reactions would be expected to become independent of $[OH^-]$ at pH 8 when the bulk of the complex was converted to the active hydroxo species. Studies of the pH dependence of a number of copper(II)-promoted reactions to such pH levels have been carried out and no evidence obtained for the production of catalytically active hydroxo complexes; however, some reactions do proceed by this pathway.

Evidence for intramolecular hydrolysis of the methyl ester (**62**) by metal hydroxide has been provided.[329] Molecular models of the metal complex (**63**) indicate that when complexation with the imidazole nitrogen and the phenolic hydroxyl group occurs, it is not possible for coordination of the ester carbonyl group to occur. This point, taken in conjunction with the observed pH rate profile which shows that ionization of the $M—OH_2$ group is associated with catalysis, eliminates metal ion activation of the carbonyl bond to intermolecular attack by OH^- as a contributing factor. For base hydrolysis of (**62**) $k_{OH} = 2.7 \times 10^{-2}\ M^{-1}\ s^{-1}$ at 25 °C. The specific rate constants for intramolecular hydrolysis by the M—OH species are $0.245\ s^{-1}$ and $2 \times 10^{-2}\ s^{-1}$ for the Co^{II} and Ni^{II} complexes respectively.



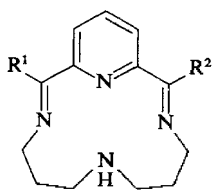
pK_1(ImH^+) 6.1
pK_2 (OH) 9.6

(62)

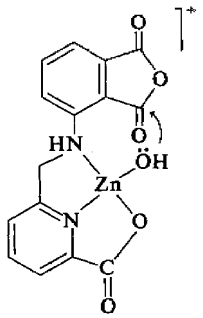


(63)

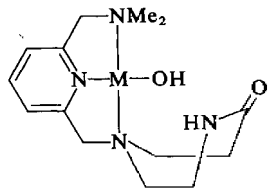
Woolley[230] has found that a number of hydroxo metal complexes of the macrocycle (**64**) are active in the hydration of CO_2 and acetaldehyde. Electronic spectroscopy[231] and X-ray crystallography[232] suggest coordination numbers in aqueous solution of five for $[CoL]^{2+}$ and $[ZnL]^{2+}$, and six for $[NiL]^{2+}$ and $[CuL]^{2+}$. For the $[ZnL]^{2+}$ system, the pK_a of the coordinated water molecule is 8.69 at 25 °C and the hydroxo complex is a reasonable catalyst for CO_2 hydration. The complex [Cu(glycylglycinate)OH] is also active in CO_2 hydration.[233]



(64) = L



(65)



(66)

Some evidence[234] for Zn—OH attack in anhydride hydrolysis has been obtained using the complex (**65**) (Section 61.4.11) but the evidence is not definitive, and other mechanisms could apply. Large rate enhancements occur in the Zn^{II}- and Cu^{II}-promoted hydrolysis of the lactam (**66**) (Section 61.4.10). Rates increase commensurate with the ionization of a metal-bound water molecular and sigmoidal pH-rate profiles are observed. Rate enhancements of 9×10^5 and 1×10^3 occur with (**66**)—Cu—OH and (**66**)—Zn—OH compared with the free ligand. A number of other reactions which are believed to proceed *via* M—OH species, in kinetically labile systems, are considered in Section 61.4.3.

61.4.4 HYDROLYSIS OF PHOSPHATE ESTERS

Phosphoryl and nucleotidyl transfer enzymes are extremely important and widespread in biology. They have in common the catalysis of nucleophilic reactions of phosphorus esters, and the general requirement for divalent metal ions, particularly Mg^{II}, for activity. This requirement has stimulated considerable interest in the catalytic roles of divalent metal ions in these reactions.

This section emphasizes work done in the last few years. The reader is referred to other sources for reviews of older work[236] or more general discussions of nucleophilic reactions at phosphorus.[237–245] More general discussions of enzymic phosphoryl and nucleotidyl transfer are available,[246–248] and the role of divalent metal ions has been reviewed.[249–251]

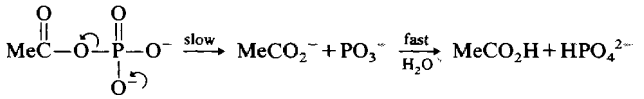
61.4.4.1 Labile Metal Ions

A variety of investigations have been carried out on metal ion-catalyzed reactions of phosphate derivatives. However, the mechanistic details are in many cases unclear.

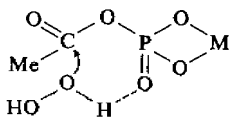
For example, a number of studies have been made on the metal ion-catalyzed hydrolyses of acetyl phosphate and acetyl phenyl phosphate,[252–257] but the role of the metal ion in these processes remains uncertain. Investigations of catalysis by exchange labile metal ions (*e.g.* Ca^{II} and Mg^{II}) have yielded conflicting results[252] and both the nature and distribution of the kinetically significant species, as well as the positions of bond cleavage, have yet to be determined unequivocally.[252,257] Chelation,[255] charge neutralization[253] and attack by metal-bound hydroxide[252] have variously been proposed as important factors in acyl phosphate hydrolysis.

The pH-independent hydrolysis of acetyl phosphate is believed[258] to be a unimolecular decomposition of $MeCO_2OPO_3^{2-}$, the substrate species, which predominates at pH > 6 (equation 21). The reaction involves P—O bond cleavage. At higher pH a reaction involving attack by OH^- on the carbonyl carbon atom becomes increasingly important.[258] The most recent work[252] on calcium(II) and magnesium(II) catalysis supports the catalytic pathways shown by the transition states (**67**)-(**69**) (M = Ca^{II} or Mg^{II}). There is an important contribution from a pathway involving reaction between MOH^+ and $MeCOPO_4M$ at high pH. In an attempt to resolve some of these mechanistic ambiguities, the exchange-inert $[Co(NH_3)_5OPO_3COMe^+]$ ion has been prepared.[259] Tracer ^{18}O studies established that base hydrolysis of coordinated acetyl phosphate ($k_{OH} = 0.53\ M^{-1}\ s^{-1}$ at 25 °C, $I = 1.0$ M) occurs with exclusive carbon–oxygen bond fission. It was also shown that the hydrolysis of acetyl phenyl phosphate monoanion is significantly catalyzed by the exchange-inert hydroxo complex $[(NH_3)_5Co—OH]^{2+}$ ($k_{MOH} = 2.9 \times 10^{-2}\ M^{-1}\ s^{-1}$ at 25 °C) which operates *via* a nucleophilic pathway involving attack at carbonyl carbon. These results indicate that attack of

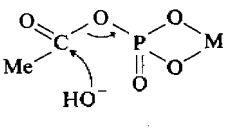
$CaOH^+$ and $MgOH^+$ on free acyl phosphate is a likely reaction pathway for Ca^{II} and Mg^{II} catalysis of the base hydrolysis of acetyl phosphate.



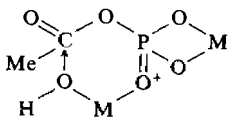
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(67)

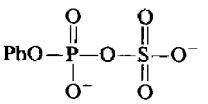


(68)



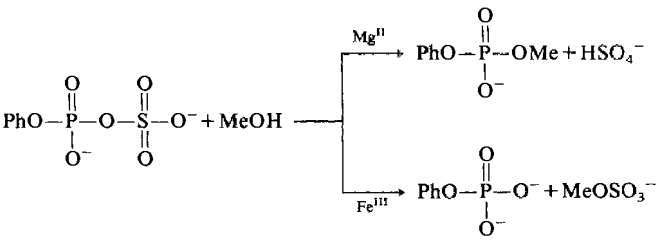
(69)

The effect of cations on the rate of hydrolysis of *cyclo*-tri- and *cyclo*-tetra-phosphates has also been studied.[260] Alkali metal cations retarded the hydrolysis of both *cyclo*-phosphates in acidic solution but accelerated the reaction in basic solution. The catalytic activity followed the sequence $Li^+ > Na^+ > K^+$. Mg^{II}, Ca^{II} and Ni^{II} retarded the hydrolysis of the *cyclo*-phosphates in the pH range 1.0–2.0 or 1.0–2.7, but accelerated the reaction at pH > 3. Catalysis by Cu^{II} is observed above pH 2, while Al^{III} has a marked catalytic effect at pH 1 and 2. A variety of other papers have appeared dealing with metal ion-promoted hydrolysis of polyphosphates.[261-264] However, the mechanistic details of these reactions remain unclear and the catalytically active complexes remain undefined.



(70)

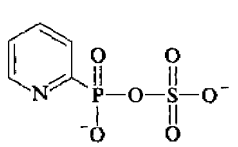
Some highly selective metal ion-promoted reactions have been observed with phenyl phosphatosulfate (**70**).[265] In both aminolysis and methanolysis reactions it was found that Mg^{II} promoted P—O bond fission, while Fe^{III} promoted S—O bond fission (Scheme 15). The selectivity is almost 100% in each case.



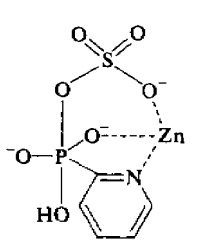
Scheme 15 Methanolysis of phenyl phosphatosulfate in the presence of Mg^{II} and Fe^{III}

Very significant zinc(II) catalysis has been observed in the hydrolysis of 2-pyridylphosphonosulfate (**71**).[266] A possible structure for the intermediate or transition state for this reaction is shown in (**72**).

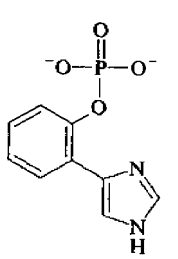
A substantial rate acceleration has also been observed for the hydrolysis of 2-(4(5)imidazoyl)phenyl phosphate (**73**) in the presence of copper(II).[267] At pH 6, a copper(II)/substrate ratio of *ca.* 2 leads to an acceleration of $>10^4$ compared to the non-catalyzed reaction. The



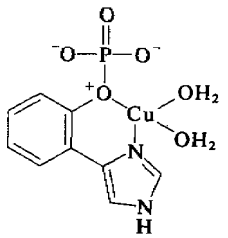
(71)



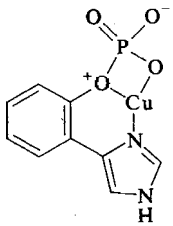
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(73)



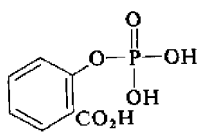
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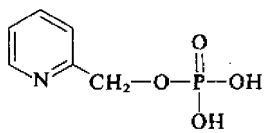
(75)

transition state in the copper(II)-promoted reaction has been formulated as (**74**) or (**75**). In (**74**) the copper(II) ion acts as a more effective acid catalyst than a proton, lowering the pK_a of the leaving group so that facile hydrolysis of the dianion (generally observed only with leaving groups of $pK_a < 7$) may be observed. In (**75**) the copper(II) is expected to induce strain in the P–O bond and/or partially neutralize charge on the phosphate, leading to nucleophilic displacement by solvent on phosphorus.

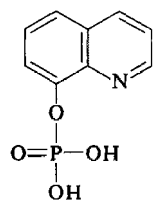
Copper(II) ions have been observed to catalyze the hydrolysis of a number of other phosphate monoesters including salicyl phosphate (**76**),[268,269,274] 2-pyridylmethyl phosphate (**77**)[270] and 8-quinolyl phosphate (**78**).[271,272,274] The catalytic effect observed with these esters was apparently quite small (*ca.* 10-fold). However, the uncatalyzed reactions of esters such as salicyl phosphate are subject to intramolecular general acid catalysis by the neighbouring carboxyl group.[273] When allowances are made for this catalysis it can be shown that copper(II) ions exert a very marked catalytic effect on the hydrolysis of the normally unreactive phosphate monoester dianion of salicyl phosphate (*ca.* 10^8 rate acceleration).[274] Intramolecular general acid catalysis occurs *via* the transition state (**79**).[273] Cleavage of the P—O bond which is well advanced is assisted by general acid catalysis by the neighbouring carboxyl group, although the proton transfer has scarcely begun. The formation of a complex such as (**80**) should lead to a similar type of transition state.



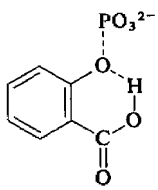
(76)



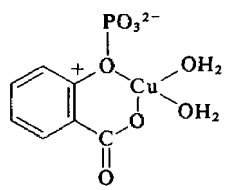
(77)



(78)

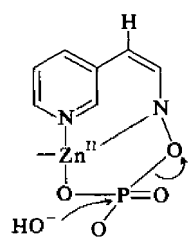


(79)

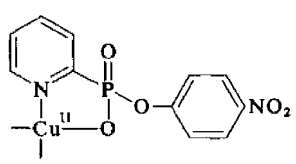


(80)

The phosphate esters (**81**) and (**82**) are also subject to catalysis by metal ions[275,276] and possible reactive complexes are illustrated. Metal complexes of adenosinediphosphoric acid and adenosinemonophosphoric acids have been studied[277] and the effect of divalent metal ions on the hydrolysis of ADP and ATP has been investigated.[278,279]



(81)



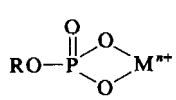
(82)

As much of biological phosphate chemistry appears to be subject to metal ion catalysis there is a great incentive to clarify and define much of the chemistry described above.

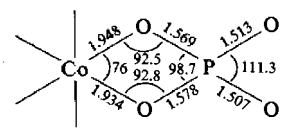
61.4.4.2 Cobalt(III) Complexes

In recent years there has been considerable interest in the hydrolytic activity of cobalt(III) complexes of phosphate esters. This approach has been adopted in order to avoid some of the mechanistic complexities which can arise with kinetically labile metal centres. Some developments in this field have been recently discussed by Dixon and Sargeson.[21]

Farrell *et al.*[280] appreciated that chelation of $ROPO_3^{2-}$ to cobalt(III) to give a four-membered chelate ring should activate the phosphorus atom towards nucleophilic attack by strain induction. Metal ion binding as in (**83**) could compress the OPO angle α in the ground state and so reduce the activation energy necessary for attainment of the trigonal bipyramidal intermediate (or transition state) in phosphoryl transfer. Similar arguments have been used to account for the high reactivity of five-membered cyclic phosphates such as ethylene phosphate.[241,281] Earlier work by Lincoln and Stranks[282] had shown that the phosphate complex $[Co(en)_2PO_4]$ existed in rapid reversible equilibrium with the monodentate complex $[Co(en)_2OH(HPO_4)]$. An X-ray study[283] of the crystal structure of $[Co(en)_2PO_4]$ establishes that the ring OPO angle (**84**) has been deformed from the unstrained tetrahedral angle of 109.5° to 98.7°, similar in magnitude to that found in methylethylene phosphate[284] (99.1°) and cytidine 2,3-cyclic phosphate (95.8°).[285]

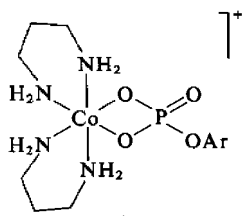


(**83**)

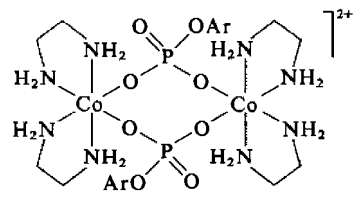


(**84**)

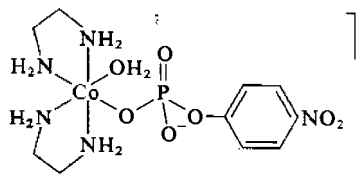
Sargeson and coworkers[283] initially reported that 4-nitrophenyl phosphate in the complex (**85**) underwent base hydrolysis some 10^9 times faster than the uncoordinated ester. Subsequent X-ray work[286] has now shown that the complex (**85**) and the analogous ethylenediamine derivative do not contain chelated phosphate esters but are dimeric species (**86**) with a surprisingly stable eight-membered chelate ring. The reactivity of such bridged complexes in basic solution has been discussed in a review.[21] The synthesis of *cis*-$[Co(en)_2(OH_2)O_3POC_6H_4NO_2]^+$ (**87**) has recently been described[287] and its hydrolysis studied over the pH range 7–14 by ^{31}P NMR spectroscopy and by monitoring nitrophenol release at 400 nm. Intramolecular attack by ^{18}O-labelled coordinated hydroxide gives initially a five-coordinate phosphorane which decays to $[Co(en)_2PO_4]$ and nitrophenol ($k_{obs} = 7.8 \times 10^{-4}\ s^{-1}$ at 25 °C in the pH range 9–11.8). The hydrolysis is 10^5 times faster than that of the uncoordinated ester under the same conditions. At pH 10 there is evidence for ^{18}O exchange between solvent and the five-coordinate phosphorane and therefore Co–OH addition and ester hydrolysis are not concerted.



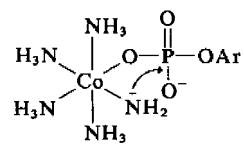
(**85**)



(**86**)



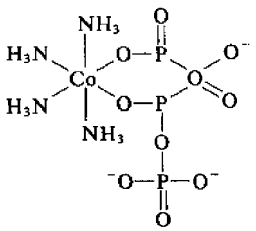
(**87**)



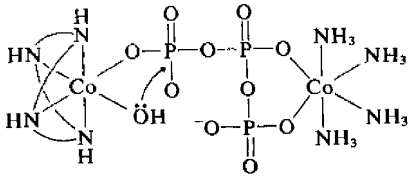
(**88**)

The base hydrolysis of $[Co(NH_3)_5O_3POC_6H_4NO_2]^+$ has also been studied.[288] In this case a coordinated aminato ion is the intramolecular nucleophile (**88**).

The hydrolysis of β,γ-$[Co(NH_3)_4H_2P_3O_{10}]$ (**89**) is greatly accelerated in the presence of *cis*-$[Co(cyclen)(OH_2)_2]^{3+}$ (Cyclen = 1,4,7,10-tetratazacyclododecane) and the intermediate (**90**) has been suggested as the active complex.[289] ^{31}P NMR studies have now provided evidence in support of such an intermediate,[290] hydrolysis occurring *via* intramolecular attack by coordinated hydroxide.



(89)



(90)

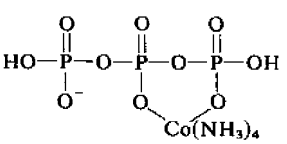
The preparation of *cis*-$[Co(cyclen)PO_4]$ has been described and its reactivity in acidic and basic solution studied.[291] This complex undergoes rapid ring opening in acidic or basic solution to give the monodentate phosphato species. Loss of monodentate phosphate in acidic solution follows a rate expression of the form $k_{obs} = k_0 + k_H[H^+]$ where $k_0 = 5 \times 10^{-4}\ s^{-1}$ and $k_H = 4.05 \times 10^{-2}\ M^{-1}\ s^{-1}$ at 25 °C ($I = 0.49$ M). Loss of monodentate phosphate from the complex $[Co(cyclen)(OH)(OPO_3)]^-$ also takes place in basic solution, and the reaction shows a first order dependence on the hydroxide ion concentration with $k_{OH} = 2.7 \times 10^{-2}\ M^{-1}\ s^{-1}$ at 25 °C and $I =$ 0.49 M. Similar studies with $[Co(en)_2PO_4]$ are also described in the paper. This work provides supporting evidence for the participation of the intermediate (**90**) in the $[Co(cyclen)(OH_2)_2]^{3+}$-promoted hydrolysis of β-γ-$[Co(NH_3)_4H_2P_3O_{10}]$. The monodentate intermediate will be sufficiently long lived in solutions of pH 8–11 to participate in the reaction.

The $[(NH_3)_5CoOP(OMe)_3]^{3+}$ ion has recently been shown[292] to react with SCN^-, I^- or $S_2O_3^{2-}$ to produce $(NH_3)_5CoO_2P(OMe)_2]^{2+}$ and respectively MeSCN, MeI or $MeS_2O_3^-$. The reactions are believed to occur by S_N2 substitution at carbon. This establishes a new mode of reaction for a coordinated phosphate ester. The rate enhancement on coordination is *ca.* 150.

The Cr^{III} and Co^{III} complexes of ATP (adenosine 5′-triphosphate) have been shown to be very good analogues for MgATP. The hydrolysis and decomposition of these complexes have now been studied in some detail.[293] The breakdown of the tridentate $[Co(NH_3)_3ATP]$ is rapid, producing high levels of free ATP and lesser amounts of ADP. Rate constants for hydrolysis are 100–5000 times greater than those for uncomplexed ATP.

Polyphosphates such as pyrophosphate and triphosphate are interesting ligands. Recently the unidentate and bidentate pyrophosphate complexes $[Co(NH_3)_5HP_2O_7] \cdot H_2O$ and $[Co(NH_3)_4HP_2O_7] \cdot 2H_2O$ have been characterized and their crystal structures determined.[294] The α,β,γ-tridentate $[Co(NH_3)_3(H_2P_3O_{10})]$ complex contains two fused six-membered chelate rings formed by the facial coordination of one O from each of the three phosphate residues.[295] The complex $[Co(NH_3)_4(H_2P_3O_{10})] \cdot H_2O$ containing the α,γ-bidentate triphosphate ligand has an eight-membered chelate ring in a boat conformation stabilized by two interligand H bonds from the axial ammines above and below the chelate ring to the β- and γ-phosphates.[296]

The rate of hydrolysis of bidentate triphosphate in $[Co(NH_3)_4H_nP_3O_{10}]$ has been studied by phosphomolybdate analysis and ^{31}P NMR.[297,298] Both the X-ray crystal structure[299] and the ^{31}P NMR spectrum of $[Co(NH_3)_4H_2P_3O_{10}]$ are consistent with structure (**91**) in which one terminal phosphate residue is not bonded to the metal centre. Kinetic studies establish that hydrolysis of the chelated ligand occurs at some two thirds of the rate for the free ligand. Hubner and Milburn[300] have noted large rate increases of *ca.* 10^5 for cobalt(III) complexes with a 3 : 1 metal : pyrophosphate stoichiometry.



(91)

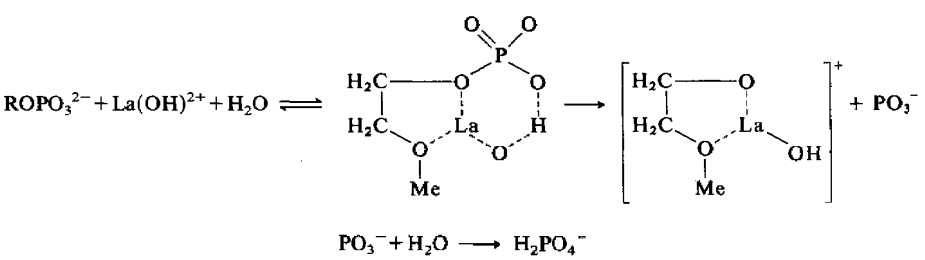
The hydrolysis of adenosine 5′-triphosphate (ATP) in the presence of various cobalt(III) complexes has been studied.[301] Complexes such as $[Co(en)_3]^{3+}$ which have no available sites for coordination of the substrate display no catalytic activity. Complexes having one site or two sites in a *trans* configuration such as tetraethylenepentaminecobalt(III) or bis(dimethylglyoximato)cobalt(III) slightly enhance ATP hydrolysis. However, complexes with two available sites in a *cis* configuration such as *cis*-α- or *cis*-β-Co(trien)$^{3+}$ exhibit considerable activity. Both the reactions $ATP + H_2O \rightarrow ADP + P_i$ and $ATP + H_2O \rightarrow AMP + PP_i$ occur with these systems. The complex $[Co(dien)]^{3+}$ effectively enhances the hydrolysis of ATP to $ADP + P_i$. At pH 4.0 the uncatalyzed hydrolysis rate constant for ATP hydrolysis is $1.18 \times 10^{-6}\ s^{-1}$ at 50 °C. For ATP (1×10^{-3} M) and $[Co^{III}(dien)]^{3+}$ (2×10^{-3} M) at pH 4.0, $k_{obs} = 1.75 \times 10^{-4}\ s^{-1}$ at 50 °C, a rate enhancement of 150-fold.

The substitution-inert complexes of chromium(III) and ATP prepared by DePamphilis and Cleland[302] have been used with considerable success to elucidate the kinetic mechanism of yeast hexokinase[303] and other enzymes.[304] Cornelius and coworkers[305] have recently isolated and characterized the complexes $[Co(NH_3)_nHATP]$ ($n = 2$, 3 or 4) and $[Co(NH_3)_nADP]$ ($n = 4$ or 5) in addition to the complexes $[Co(en)_2HP_2O_7]$, $[Co(NH_3)_nHP_2O_7]$ ($n = 4$ or 5) and $[Co(NH_3)_nH_2P_3O_{10}]$ ($n = 3$ or 4). The ^{31}P NMR spectra of the simpler phosphato complexes provide definitive evidence of pyrophosphate both as a monodentate and as a bidentate ligand, and of tripolyphosphate both as a bidentate and as a tridentate ligand. A correlation between OPO bond angles and the ^{31}P NMR chemical shift for a number of phosphate esters has been noted.[306] If such a correlation could be extended to cobalt(III) complexes, ^{31}P NMR would be a powerful tool for determining the solution geometry of phosphates bound to cobalt.

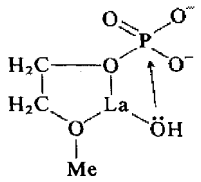
Clearly important results and developments are to be expected in this experimentally difficult area.

61.4.4.3 Metal Hydroxide Gels

A number of studies have been reported on the hydrolysis of phosphate esters by metal hydroxide gels.[307–309] In view of the heterogeneous nature of these reactions it is difficult to come to firm mechanistic conclusions; however, it seems likely that metal-bound nucleophiles are probably involved. Bamann[308] first noted that the hydroxides of lanthanum, cerium and thorium promoted the hydrolysis of α-glycerophosphate in the pH range 7–10 and suggested that the reaction could be regarded as a model for the metal-containing alkaline phosphatases which cleave phosphate esters around pH 9. When the ester is adsorbed on the hydroxide gel, the cation neutralizes the negative charges on the phosphate dianion $ROPO_3^{2-}$ and allows more facile attack by hydroxide ion. Butcher and Westheimer[310] have investigated similar reactions of this type and have found that the process resembles the enzymatic reaction in that cleavage occurs exclusively at the phosphorus–oxygen bond. The reaction does not occur readily unless the phosphate ester is substituted in the β-position, so that the hydrolysis of ethyl phosphate is not greatly promoted by lanthanum hydroxide gel, but the hydrolysis of β-methoxyethyl, β-hydroxyethyl and β-aminoethyl phosphates is strongly catalyzed at pH 8.5 and 78 °C. The hydrolysis of β-methoxyethyl phosphate is regarded as occurring by the steps shown in Scheme 16. The ester 1-methoxy-2-propyl phosphate is hydrolyzed at pH 4, or by $La(OH)_3$ at pH 8.5 with complete retention of stereochemical configuration and P–O bond cleavage. Catalysis by rare earth ions has been discussed by Trapmann.[311] Scheme 16 was suggested prior to the recognition of the high reactivity of metal-bonded OH species in hydrolysis. Hydrolysis *via* a complex of type (**92**) could provide a very reactive pathway.



Scheme 16



(92)

61.4.5 REACTIONS OF COORDINATED NITRILES

In recent years there has been considerable interest in the reactions of nitriles in the coordination sphere of metal ions. Breslow *et al.*[312] first reported that the hydrolysis of 2-cyano-1,10-phenanthroline to the corresponding carboxamide is strongly promoted by metal ions such as copper(II), nickel(II) and zinc(II). Base hydrolysis of the 1:1 nickel complex is 10^7 times faster than that of the uncomplexed substrate. The entire rate acceleration arises from a more positive value of ΔS^{+}. Somewhat similar effects have been observed for base hydrolysis of 2-cyanopyridine to the corresponding carboxamide. In this case rate accelerations of 10^9 occurred with the nickel(II) complex.[313]

A number of studies have also been made of the hydrolysis of nitriles in the coordination sphere of cobalt(III). Pinnell *et al.*[314] found that benzonitrile and 3- and 4-cyanophenol coordinated to pentaamminecobalt(III) are hydrolyzed in basic solution to the corresponding N-bonded carboxamide (equation 22). The reaction is first order in hydroxide ion and first order in the complex with $k_{OH} = 18.8\ M^{-1}\ s^{-1}$ at 25.6 °C for the benzonitrile derivative. As k_{OH} for the base hydrolysis of benzonitrile is $8.2 \times 10^{-6}\ M^{-1}\ s^{-1}$ at 25.6 °C, the rate acceleration is *ca.* 2.3×10^6-fold. The product of hydrolysis is converted to $[(NH_3)_5CoNH_2COPh]^{3+}$ in acidic solution and the pK of the protonated complex is 1.65 at 25 °C. Similar effects have been observed with aliphatic nitriles.[315] Thus, base hydrolysis of acetonitrile to acetamide is promoted by a factor of 2×10^6 on coordination to $[Co(NH_3)_5]^{3+}$.

$$[(NH_3)_5CoN{\equiv}CPh]^{3+} + OH^- \xrightarrow{k_{OH}} [(NH_3)_5CoNHC(=O)Ph]^{2+} \qquad (22)$$

Particular emphasis has been directed towards comparison of ligand properties and reactions of different organonitrile complexes of the type $[M(NH_3)_5(NCR)]^{n+}$ where $M = Ru^{II}$, Ru^{III}, Rh^{III} or Ir^{III}.[337] Specific rates of base hydrolysis of the pentaammineruthenium(III) complexes of acetonitrile ($k_{OH} = 2.2 \times 10^2\ M^{-1}\ s^{-1}$ at 25 °C) and of benzonitrile ($k_{OH} = 2.0 \times 10^3\ M^{-1}\ s^{-1}$) are some 10^8 times faster than the free ligand, and about 10^2 times faster than the analogous cobalt(III) complexes.[316] The reaction products are the corresponding amido complexes which reversibly protonate in acidic solution to give the amide complexes. Base hydrolysis of the pentaamminerhodium(III) complex of acetonitrile ($k_{OH} = 1.0\ M^{-1}\ s^{-1}$)[316,337] occurs at a rate comparable to that of the analogous cobalt(III) complex, while the ruthenium(II) complex is at least 10^6 times less reactive than the corresponding ruthenium(III) complex. Representative kinetic data for these reactions are summarized in Tables 20 and 21.

Table 20 Rate Constants (k_{OH}) and Activation Parameters for the Base Hydrolysis of Nitriles to Carboxamides

Substrate	k_{OH} ($M^{-1}\ s^{-1}$)	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J $K^{-1}\ mol^{-1}$)
MeCN	1.6×10^{-6}	77.4	−96
PhCN	8.2×10^{-6}	80.8	−63
$[(NH_3)_5CoN{\equiv}CMe]^{3+}$	3.4	75.3	+17
$[(NH_3)_5RhN{\equiv}CMe]^{3+}$	1.0		
$[(NH_3)_5RuN{\equiv}CMe]^{3+}$	2.2×10^2		
$[(NH_3)_5IrN{\equiv}CMe]^{3+}$	0.23		
$[(NH_3)_5RuN{\equiv}CMe]^{2+}$	$<6 \times 10^{-5}$		
$[(NH_3)_5CoN{\equiv}CPh]^{3+}$	18.8	69.0	+13
$[(NH_3)_5RuN{\equiv}CPh]^{3+}$	2.0×10^3		
$[(NH_3)_5CoN{\equiv}CC_6H_4O\text{-}p]^{2+}$	0.2	66.9	−29
$[(NH_3)_5CoN{=}CCH{=}CH_2]^{3+}$	35		
$[(NH_3)_5CoN{=}CNMe_2]^{3+}$	3.06		

[a] Data from ref. 21, and N. J. Curtis and A. M. Sargeson, *J. Am. Chem. Soc.*, 1984, **106**, 625.

Table 21 Base Hydrolysis of Nitrile Complexes[a]

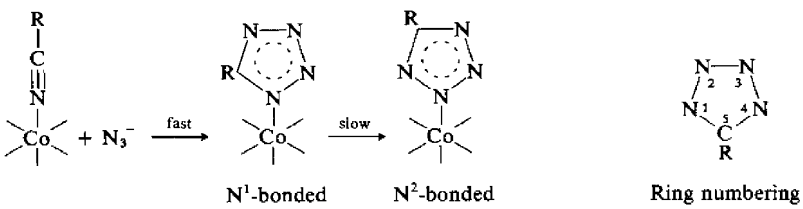
Nitrile	k_{OH} ($M^{-1}s^{-1}$)	*Relative Rate*
MeCN	1.60×10^{-6}	1.0
$[(NH_3)_5Ru(MeCN)]^{3+}$	2.2×10^{2}	1.4×10^{8}
$[(NH_3)_5Rh(MeCN)]^{3+}$	1.0	6.2×10^{5}
$[(NH_3)_5Co(MeCN)]^{3+}$	3.40	2.12×10^{6}
$[(NH_3)_5Ru(MeCN)]^{2+}$	$<6\times10^{-5}$	<38
PhCN	7.2×10^{-6}	1.0
$[(NH_3)_5Ru(PhCN)]^{3+}$	2.0×10^{3}	2.8×10^{8}
$[(NH_3)_5Co(PhCN)]^{3+}$	18.2	2.53×10^{6}
2-Cyanophenanthroline	2.6×10^{-3}	1.0
[(2-Cyanophenanthroline)Ni]$^{2+}$	2.4×10^{4}	10^{7}

[a] Data from A. W. Zanella and P. C. Ford, *Inorg. Chem.*, 1975, **14**, 42 and D. A. Buckingham, F. R. Keene and A. M. Sargeson, *J. Am. Chem. Soc.*, 1973, **95**, 5649.
[b] At 25 °C; $I = 1.0$ M except for Ru^{II}.
[c] Relative rate = k_{OH} (complex)/k_{OH} (free ligand)

With the exception of the Ru^{II} complex, a variety of metal ions activate the hydration reaction to a very consistent extent (10^6-10^8-fold). The relative constancy of the rate acceleration and the anomaly of the Ru^{II} complex are consistent with the view that it is the Lewis acidity of the metal ion which is essential for activation. In the Ru^{II} complex, considerable metal→ligand π-bonding is expected, resulting in back donation of electron density from the metal centre into the C≡N bond. This view is supported by measurements of the C≡N stretching frequency of free nitriles and of their complexes with Ru^{II} and the other metal ions.[317]

In addition to OH^-, other nucleophiles such as BH_4^-,[318] CN^-[319,320] and N_3^-[321] also add at the nitrile carbon of cobalt(III)-nitrile complexes at rates which are $\geq10^4$ times those of the corresponding reactions of the free ligands. Catalysis by CO_3^{2-} in the hydration of $[(NH_3)_5RuNCMe]^{3+}$,[316] and of the acrylonitrile complex $[(NH_3)_5CoNCCH{=}CH_2]^{3+}$,[322] has been observed. In the latter complex, a direct nucleophilic pathway results in the incorporation of oxygen from CO_3^{2-} into the amide product with elimination of CO_2.

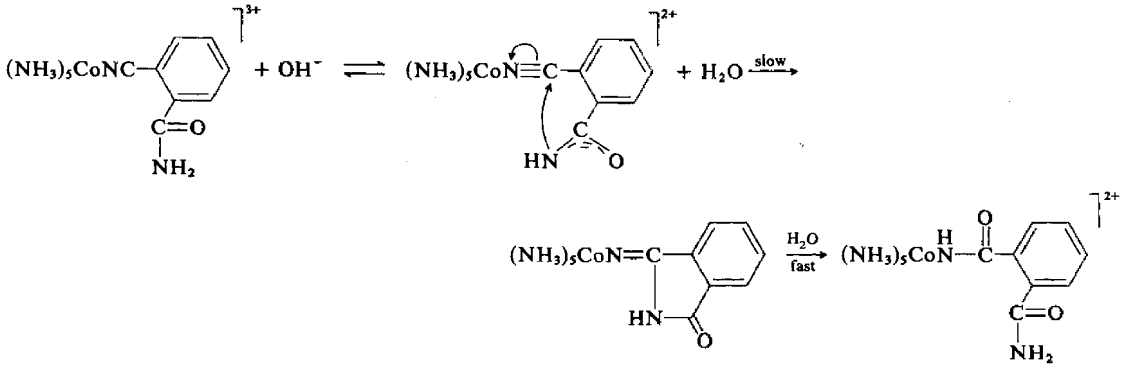
When aqueous solutions of the complexes $[Co(NH_3)_5(N{\equiv}CR)]^{3+}$ (R = Me or Ph) are treated with an excess of NaN_3 at pH 5-6 (to prevent base hydrolysis to the amido complex) tetrazole complexes are formed (Scheme 17).[321] The formation of 5-methyltetrazole from sodium azide and acetonitrile requires a reaction time of 25 h at 150 °C[323] compared with only 2 h at ambient temperature for coordinated acetonitrile. The subsequent conversion of the N^1-bonded complex to an N^2-bonded complex has been confirmed as the latter complex has been prepared and its crystal structure determined.[324]



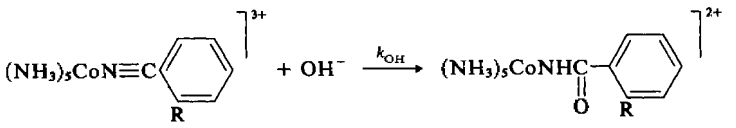
Scheme 17

Coordination of malononitrile, cyanoacetic acid and ethyl cyanoacetate to the $[(NH_3)_5Co]^{3+}$ group leads to greatly increased acidity of the methylene protons. Thus the pK_a of the coordinated malononitrile is 5.7 compared with 11.3 for the free ligand at 25 °C.[322] The protonated complexes are hydrolyzed to coordinated nitriles by both water and hydroxide ion acting as nucleophiles. The deprotonated complexes undergo intramolecular electron transfer to give Co^{II} and the ligand radical, and also act as nucleophiles towards appropriate substrates (methyl iodide, methyl pyruvate or bromine) to give the corresponding substituted species.

Neighbouring-group participation in the hydrolysis of coordinated nitriles has also been investigated.[325] The hydrolysis of (**93**) has been studied for R = H ($k_{OH} = 1050\ M^{-1}s^{-1}$, $\Delta H^{+} = 56.9$ kJ mol^{-1}, $\Delta S^{+} = 4$ J K^{-1} mol^{-1}) and R = $CONH_2$ ($k_{OH} = 5.8\times10^{6}\ M^{-1}s^{-1}$, $\Delta H^{+} = 69.1$ kJ mol^{-1}, $\Delta S^{+} =$ J K^{-1} mol^{-1} at 25 °C). The unusual kinetic parameters for the latter reaction are attributed to neighbouring group participation by the amide group (Scheme 18). Rate constants

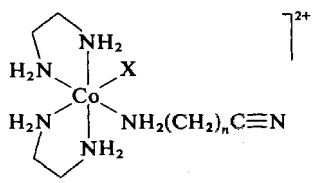


Scheme 18



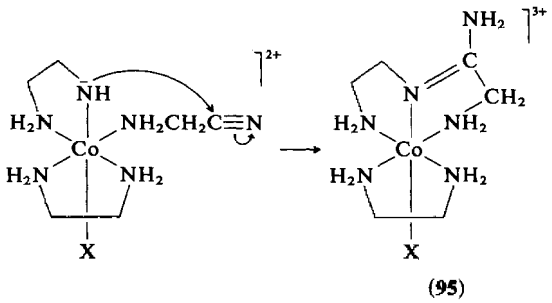
(**93**)

for the hydrolysis of 11 coordinated substituted aromatic nitriles have been found to follow a Hammett-type relationship with log $k_{OH} = 1.93\sigma + 1.30$ at 25 °C.[326] Interestingly, ^{13}C NMR studies of the nitrile carbon chemical shift in these complexes and in the corresponding free ligands show little variation, suggesting that the rate accelerations arise from transition state effects and not from ground state effects.



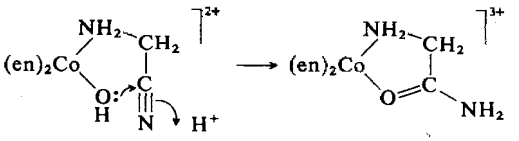
(**94**) $n = 2$- or 3
X = Cl, Br

A variety of interesting investigations have been made using complexes of type (**94**). In near neutral or basic solution, the complex containing aminoacetonitrile (**94**; $n = 1$) undergoes rapid base-catalyzed ring closure to give the purple complex (**95**) containing the tridentate amidine ligand (Scheme 19).[327,328,336] For X = Cl, $k_{OH} = 2.6 \times 10^4$ M^{-1} s^{-1} at 25 °C and $I = 0.1$ M.[328] Condensation occurs *via* the nitrogen centre *trans* to the halide ion.[327] Treatment of *cis*-$[Co(en)_2(NH_2CH_2CN)X]^{2+}$ ions (X = Cl or Br) with Hg^{II} results in the formation of both $[Co(en)_2(GlyNH_2)]^{3+}$ and $[Co(en)_2(NH_2CH_2CONH)]^{2+}$, the product ratio depending on the leaving group.[328,329] Similar treatment of *cis*-$[Co(en)_2(NH_2CH_2CH_2CN)Br]^{2+}$ gives *cis*-$[Co(en)_2(NH_2CH_2CH_2CN)OH_2]^{3+}$ initially which ring closes to $[Co(en)_2(\beta\text{-AlaNH}_2)]^{3+}$. The reaction (Scheme 20) has $k = 1.15 \times 10^{-2}$ s^{-1} so that the reaction occurs *ca.* 10^{11} times more rapidly than intermolecular hydration of free acetonitrile by OH^- ($k_{OH} = 1.6 \times 10^{-6}$ M^{-1} s^{-1}). Further enhancement of the rates of the reactions of both the aminoacetonitrile and aminopropionitrile complexes by factors of 10^6 occurs in the presence of 1 M Hg^{II}. Additional activation also occurs

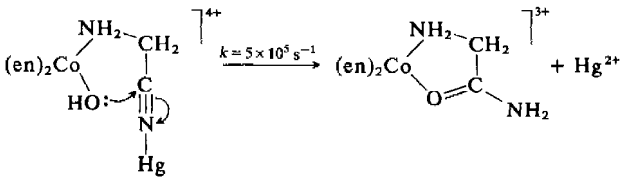


(**95**)

Scheme 19



Scheme 20



Scheme 21

with Ag^{I}, Zn^{II} and Cd^{II}. Presumably these ions interact with the nitrile nitrogen (Scheme 21). The concerted action of two metal centres, one providing an intramolecular nucleophile and the other acting as an electrophile, can produce extraordinarily efficient catalysis.

Previous work has shown that the base hydrolysis of organonitriles is increased by a factor of *ca.* 10^8 on coordination to pentaaminеruthenium(III) and by about 10^6 on coordination to Co^{III} and Rh^{III}. A base-independent pathway is also observed with Ru^{III}, due to water attack on the coordinated nitrile.[330] The relative nucleophilicities of hydroxide ion and water for attack on *N*-coordinated nitriles are *ca.* 10^9 (Table 22).

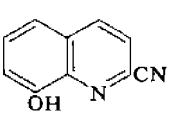
Table 22 Rate Constants for Base Hydrolysis and Water Hydrolysis of $[Ru(NH_3)_5N{\equiv}CR]^{3+}$ Complexes

Nitrile	k_{OH} ($M^{-1}s^{-1}$)	k_{H_2O}[b] ($M^{-1}s^{-1}$)	k_{OH}/k_{H_2O}
Acetonitrile	2.2×10^2	2.2×10^{-7}	10^9
Benzonitrile	2.0×10^3	6.1×10^{-7}	3×10^9

[a] Data from B. Anderes and D. K. Laralee, *Inorg. Chem.*, 1983, **22**, 3724.
[b] The observed first order rate constants are 1.2×10^{-5} s^{-1} (acetonitrile) and 3.4×10^{-5} s^{-1} (benzonitrile). These constants have been converted to second order rate constants by dividing by the molar concentration of water (55.5 M).

In addition to studies with inert metal complexes, some interesting measurements have been made with labile metal ions. Metal ions such as Ni^{II}, Co^{II} and Cu^{II} have been found to strongly promote the base hydrolysis of 2-cyano-8-hydroxyquinoline (**96**) to the corresponding carboxamide.[331] For the free ligand $k_{OH} = 4.85\times10^{-3}$ M^{-1} s^{-1} at 45 °C and $I = 1.0$ M. The 1:1 complex of nickel(II) and 2-cyano-8-hydroxyquinoline undergoes base hydrolysis 2×10^5 times faster than the free ligand at 45 °C. Activation parameters (Table 23) indicate that the substantial rate accelerations are due to an entropy effect, a result also observed with 2-cyanophenanthroline.[312] For steric reasons bonding of the cyano group to the metal ion cannot occur in the initial state of the reaction with these ligands. It therefore appears that the transition state must involve bonding of the developing imino anion to the metal ion possibly resulting in the displacement of a coordinated water molecule (Scheme 22, reaction A). The metal ion can be regarded as 'solvating' the developing negative charge on the nitrogen atom of the cyano group. These effects would lead to more positive entropies of activation and thus account for the observed rate accelerations. Intramolecular attack by coordinated hydroxide (Scheme 22, reaction B) does not appear to play a part in this reaction.[331]

The activation parameters in Table 20 show that entropy effects account for the complete rate acceleration observed in the base hydrolysis of $[Co(NH_3)_5N{\equiv}CMe]^{3+}$. Similar transition state

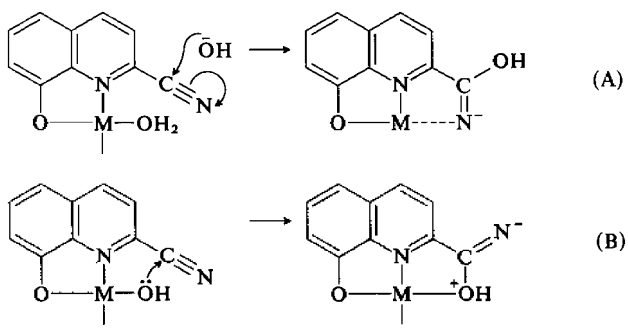


(**96**)

Table 23 Rate Constants and Activation Parameters for Base Hydrolysis of Nitriles and Nitrile Complexes

Nitrile	k_{OH} ($M^{-1}\,s^{-1}$)	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J $K^{-1}\,mol^{-1}$)
Benzonitrile	8.2×10^{-6} [a]	83.3	−63.6
$[(NH_3)_5Co(PhCN)]^{3+}$	18.8[a]	69.0	11.3
2-Cyano-1,10-phenanthroline	2.6×10^{-3} [a]	65.7	−84
$[Ni(2\text{-cyano-}1,10\text{-phenanthroline})]^{2+}$	2.4×10^{4} [a]	63.2	59
$[Ni(2\text{-cyanopyridine})]^{2+}$	6.3×10^{7} [a]	57.3	96
2-Cyano-8-hydroxy-quinolinate	4.85×10^{-3} [b]	56.1	−113
[Ni(2-cyano-8-hydroxy-quinolinate)]$^{+}$	7.97×10^{2} [b]	59.4	−41.0
[Co(2-cyano-8-hydroxy-quinolinate)]$^{+}$	2.74×10^{2} [b]	59.8	−13

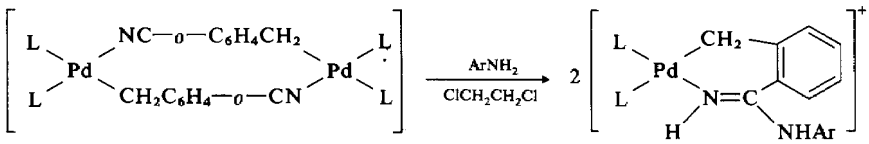
[a] Data from D. Pinnell, G. B. Wright and R. B. Jordan, *J. Am. Chem. Soc.*, 1972, **94**, 6104 (25 °C).
[b] Data from C. R. Clark and R. W. Hay, *J. Chem. Soc., Dalton Trans.*, 1974, 2148 (45 °C).



Scheme 22

effects probably occur in these inert metal systems, a view supported by further recent experimental evidence.[326]

The metal-bound RCN group is also activated on coordination towards nucleophilic attack by alcohols, thiols or amines to give stable N-bonded iminoether, iminothioether and amidine complexes respectively.[332] Several cationic cyanobenzylpalladium(II) complexes have been prepared, and the reactivity of the CN group towards nucleophiles has been studied.[333,334] The palladium complex (**97**) reacts with aromatic amines to give chelated amidino complexes (**98**) and the reaction has been studied kinetically.[335] In this case intermediates with the nitrile group bonded 'side-on' are considered to be involved.



(**97**) (**98**)

61.4.6 DECARBOXYLATION OF β-OXO ACIDS

Some of the earliest kinetic studies on metal ion-promoted reactions were carried out on metal ion-promoted decarboxylations of β-oxo acids. The literature on this topic up to about 1974 has been reviewed.[338] Much of the work has centred on oxaloacetic acid ($HO_2CCOCH_2CO_2H$ = H_2oxac) and its derivatives, α,α-dimethyl oxaloacetic acid[341] and fluorooxaloacetic acid.[342] Studies have also been made with acetonedicarboxylic acid (3-oxoglutaric acid),[343-345] dihydroxyfumaric acid,[346] dihydroxytartaric acid,[347] acetosuccinic acid,[348] oxalosuccinic acid[349] and 2-oxalopropionic acid[340] (Figure 6). The decarboxylation of β-oxo acids is of considerable biological importance, and in a number of cases metalloenzymes are involved. Similarities in the enzymatic and chemical processes stimulated early interest in these reactions as models for the enzymatic systems.

Some 25 papers have been published on various aspects of the metal ion-promoted decarboxylation of oxaloacetic acid and its derivatives[338-340] and this system can be used to illustrate many features of these reactions. The β-oxo acids decarboxylate spontaneously in aqueous solution

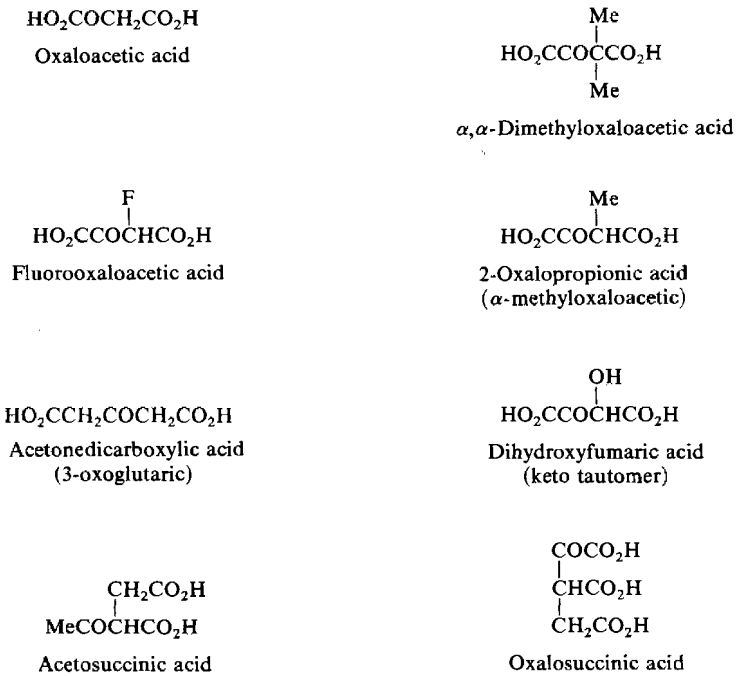
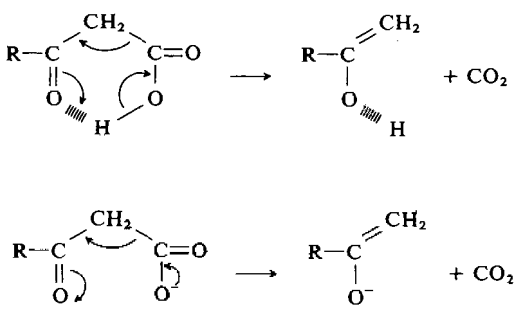


Figure 6 Structures of β-oxo acids which are subject to metal ion-promoted decarboxylation



Scheme 23

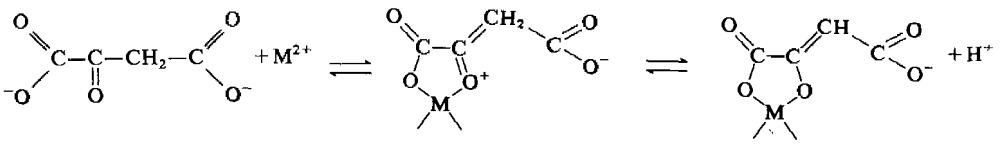
(Scheme 23). An enol or an enolate ion intermediate is involved in the process, the intermediate subsequently ketonizing (equation 23).

$$RC(O^-)=CH_2 + H^+ \rightleftharpoons RC(OH)=CH_2 \rightarrow RC(=O)Me \qquad (23)$$

Pedersen[350] showed that α,α-dimethylacetoacetic acid cannot enolize decarboxylates readily and thus concluded that the keto tautomers of β-oxo acids are kinetically unstable. The enol intermediate formed in the decarboxylation of β-oxo acids has been trapped by reaction with bromine[351] and has also been detected spectrophotometrically in the decarboxylation of α,α-dimethyloxaloacetic acid,[341] oxaloacetic acid[352] and fluorooxaloacetic acid.[342]

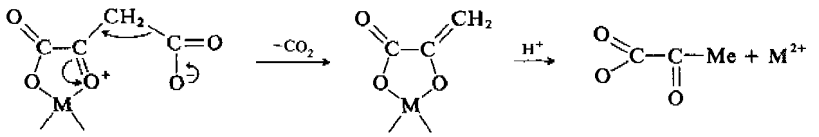
The instability of the β-oxo acids is a result of the electron-withdrawing carbonyl group which acts as an 'electron sink' for the pair of electrons withdrawn from the carbon-carbon bond undergoing cleavage. Other electron-withdrawing groups such as nitro and trichloromethyl groups act in a similar manner.[353]

The decarboxylation of simple monofunctional β-oxo acids such as acetoacetic acid ($MeCOCH_2CO_2H$) is not catalyzed by metal ions and a necessary prerequisite for metal ion catalysis is the presence of an additional functional group, in the δ-position to the labile carboxyl group which is capable of interacting with metal ions. All of the acids which are subject to metal ion catalysis (Figure 6) have an α-carboxyl group, so that formation of a five-membered chelate ring involving the carbonyl group of the acid can occur. The various equilibria involved with



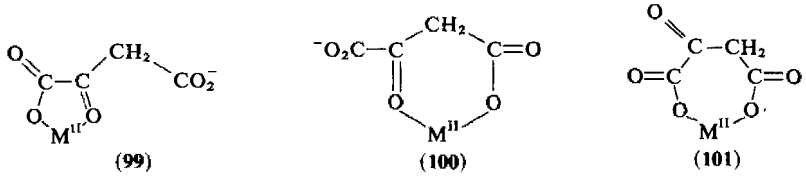
ketonic complex enolic complex

Scheme 24 Equilibria involved with oxaloacetic acid



Scheme 25 Metal-promoted decarboxylation

oxaloacetic acid are shown in Scheme 24. The ketonic complex is the active species in the decarboxylation decomposing to give an enolic intermediate which subsequently ketonizes as shown in Scheme 25. In addition to the α-oxo carboxylate complex (**99**), the β-oxo carboxylate complex (**100**) and the dicarboxylate complex (**101**) could also form with oxaloacetic acid and its derivatives. NMR isotropic shifts of the CH_2 group of the europium oxaloacetate provide evidence for the formation of the α-oxo carboxylate complex as the main species in solution.[354] Covey and Leussing[339] also found that the five-membered ring structure (**99**) predominates with Zn^{II} and oxaloacetic acid but suggested that 10–20% of the complex was present as the seven-membered chelate ring (**101**) in which both carboxylate functions are coordinated to Zn^{II}. Kubala and Martell[355] have proposed, on the basis of potentiometric studies, that five-membered ring chelates are the major constituents with metal ions and 2-oxalopropionic acid (α-methyl oxaloacetic acid), but that six-membered rings such as (**100**) may be present to the extent of some 15%.



(**99**) (**100**) (**101**)

For the decarboxylation of oxaloacetic acid the reactions shown in Scheme 26 can be considered. Early measurements of rate constants (k) and formation constants (K_{MA}) are summarized in Table 24. The copper complex CuA decarboxylates some 9.4×10^2 times faster than the dianion A^{2-}.

$$M^{2+} + A^{2-} \overset{K_{MA}}{\rightleftharpoons} MA$$

$$MA \xrightarrow{k} \text{products}$$

Scheme 26

Table 24 Rate Constants and Formation Constants for Metal Oxaloacetates at 37 °C and $I = 0.1$ M[a]

Species	$10^3\,k$ (min^{-1})	$\log K_{MA}$
H_2A	0.345	—
HA^-	15.4	—
A^{2-}	4.2	—
CaA	144	2.6
MnA	390	2.8
CoA	1440	3.1
ZnA	1860	3.2
NiA	1380	3.5
CuA	3960	4.9

[a] The rate constants for the uncatalyzed decarboxylation are from E. Gelles, *J. Chem. Soc.*, 1956, 4736, and for the catalyzed decarboxylation from E. Gelles and A. Salama, *J. Chem. Soc.*, 1958, 3689. Formation constants from E. Gelles and A. Salama, *J. Chem. Soc.*, 1958, 3683.

Covey and Leussing[339] have subsequently carried out detailed studies of the zinc(II)-catalyzed decarboxylation of oxaloacetate. Two processes are observed using stopped flow techniques: an initial absorbance increase being complete in about 30 s and a subsequent absorbance decrease being complete after 15 to 30 min. The first process is due to metal ion-promoted keto–enol tautomerism and the second to catalyzed decarboxylation. The subsequent protonation of the zinc pyruvate intermediate is rapid and unobservable. The rate constant for the decarboxylation of $Zn(oxac)_{keto}$ is 7.42×10^{-3} s^{-1} at 25 °C and $I = 0.1$ M compared with the rate constant 31×10^{-3} s^{-1} previously reported at 37 °C (Table 24). Detailed studies of the copper(II)-promoted decarboxylation have also been published.[356] The reaction scheme in this case is summarized in Scheme 27. The release of CO_2 is biphasic as is also the rate of H^+ uptake in the step where pyruvate is formed. Only about 20% of the $oxac^{2-}$ in the system undergoes decarboxylation within the first 30 s. The remaining 80% is present as $Cu(oxac)_{enol}$ which does not decarboxylate. The slow rate of CO_2 evolution arises from the decarboxylation of a residual level of $Cu(oxac)_{keto}$ which is replenished by reketonization of $Cu(oxac)_{enol}$. For the decarboxylation $Cu(oxac)_{keto} \rightarrow CO_2 + Cu(pyruvate)_{enolate}$, $k = 0.17$ s^{-1} at 25 °C and $I = 0.1$ M so that the copper(II) complex decarboxylates some 23 times faster than the zinc complex.

$$Cu(oxac)_{enol} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} Cu(oxac)_{keto} \xrightarrow[k_{CO_2}]{-CO_2} Cu(pyruvate)_{enolate} \xrightarrow[k_H]{H^+} Cu(pyruvate)$$

Scheme 27

The keto–enol tautomerism rates for oxaloacetate and zinc(II)-oxaloacetate have also been investigated using acetate buffer solutions.[339,357] Thus for the equilibrium shown in equation (24) the value of k_f for the reaction $oxac_{keto}^{2-} + OAc^-$ is 6.6×10^{-3} M^{-1} s^{-1}, while for $Zn(oxac)_{keto} + OAc^-$, $k_f = 25$ M^{-1} s^{-1}. The rate acceleration at 25 °C is *ca.* 4×10^3. Metal ion-promoted enolization is considered in detail in Section 61.4.20.

$$oxac_{keto}^{2-} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} oxac_{enol}^{2-} \tag{24}$$

The recent work by Leussing and his coworkers provides a good example of the mechanistic complexities which can occur in reactions of this type. Detailed studies of the influence of glycine, alanine, histidine, glycylglycine, imidazole and phen on the Cu(II)-catalyzed decarboxylation and enolization of oxaloacetate have also been described.[358] At amine concentrations comparable to those of the metal ion, large rate enhancements of decarboxylation are observed under certain conditions, due to the formation of mixed ligand complexes. The ternary complex [Cu(phen)(oxac)] is particularly active presumably due to back π-bonding which increases the Lewis acidity of the metal centre. A variety of other studies on the reactivity of mixed ligand complexes of β-keto acids have been published.[338,359,360]

The Zn^{II}-, Al^{III}- and Cu^{II}-catalyzed decarboxylation of 2-oxalopropionic acid ($HO_2CCOCH(Me)CO_2H$) has recently been investigated in detail.[340] Rate constants (k_{ML}) for the decarboxylation of ZnL, CuL and AlL^+ were found to be 18.2×10^{-3}, 21.0×10^{-3} and 9.51×10^{-3} s^{-1} respectively at 25 °C. The equilibrium constants for ML(keto) $\rightleftharpoons$ ML(enol) were obtained for the Zn^{II} and Al^{III} systems and the rate constants for the decarboxylation of the active keto forms of the Zn^{II} and Al^{III} complexes were found to be 31×10^{-3} and 79×10^{-3} s^{-1} at 25 °C.

61.4.7 ORGANOSULFUR COMPOUNDS

Soft metal ions such as Hg^{II} and Ag^{I} have long been known to react readily with organo sulfur compounds, and a review of the metal ion-promoted reactions which can occur is available.[17]

The hydrolysis of thiol esters[361] (equation 25), thione esters[362] (equation 26) and thiolbenzimidate esters[363] (equations 27 and 28) are all strongly promoted by Hg^{II} in aqueous solution at pH < 3

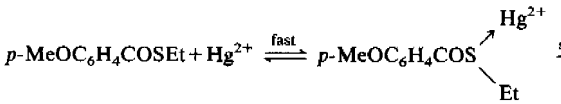
$$p\text{-}RC_6H_4COSEt + Hg^{2+} + 2H_2O \rightarrow p\text{-}RC_6H_4CO_2H + H_3O^+ + HgSEt \tag{25}$$

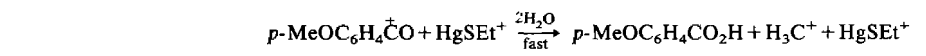
$$p\text{-}RC_6H_4CSOEt + Hg^{2+} + 2H_2O \rightarrow p\text{-}RC_6H_4CO_2Et + 2H_3O^+ + HgS \tag{26}$$

$$PhC(=\overset{+}{N}H_2)SEt + Hg^{2+} + 2H_2O \rightarrow PhCN + 2H_3O^+ + HgSEt^+ \tag{27}$$

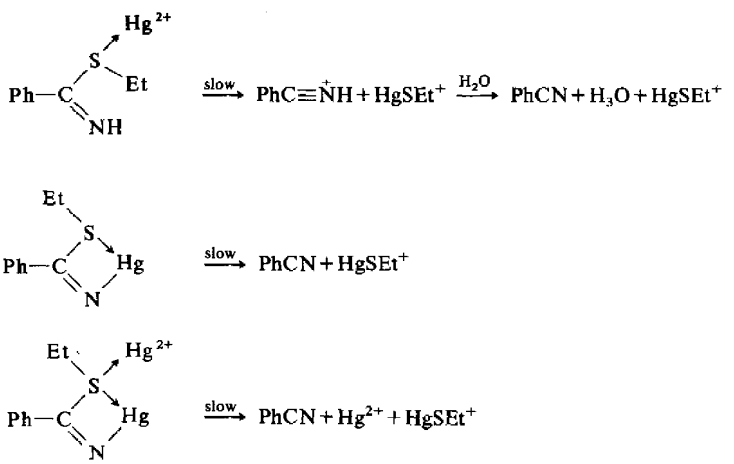
$$PhC(=\overset{+}{N}H_2R')SEt + Hg^{2+} + 3H_2O \rightarrow PhCONHR' + 2H_3O^+ + HgSEt^+ \tag{28}$$

at 25 °C where proton-catalyzed reactions are of negligible importance. For equation (25) where R = OMe, the reaction follows an A-1 pathway (Scheme 28), but an A-2 pathway applies when $R = NO_2$. An A-1 mechanism is also observed for the hydrolysis shown in equation (27). Three slow unimolecular product-forming steps have been identified (Scheme 29). For all of these reactions[361-363] only a small amount of pre-equilibrium complex formation occurs. In these S-ester reactions Hg^{II} and Ag^{I} are usually *ca.* 10^6-fold and 10^3-fold, respectively, more effective than the proton. Ions such as Tl^{III} and $[AuCl_4]^-$ have also been shown to be of comparable activity to Hg^{II} in the S-imidate hydrolysis and are presumably also very efficient with other types of S-esters. Other rather soft metal ions such as Cd^{II}, Cu^{II} and Pb^{II} have very limited effects at pH ≤ 3 and are probably less effective than the proton.





Scheme 28



Scheme 29



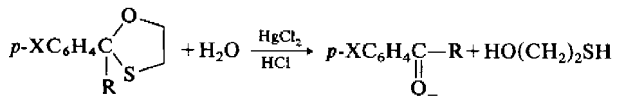
(102) **(103)** **(104)** **(105)**

Thiols, like alcohols, react readily with carbonyl compounds. The resulting hemithioacetals (**102**), thioacetals (**103**) and their cyclic analogues (**104**) and (**105**) are of considerable synthetic importance. These compounds are more stable to acid hydrolysis than their oxygen analogues but can be hydrolyzed under mild conditions in the presence of metal ions such as Ag(I) (equation 29). The synthetic importance of the metal ion-promoted hydrolyses has led to the publication

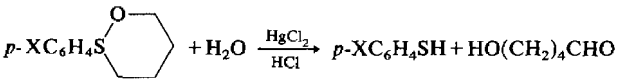
$$R_2C(SR')_2 + 2Ag^+ + 3H_2O \rightarrow RCOR + 2R'SAg + 2H_3O^+ \qquad (29)$$

of a variety of preparative procedures.[364-366] These procedures mainly involve salts or oxides of soft metals, but little kinetic work has been carried out and the mechanistic details are unclear. Some kinetic work on the hydrolysis of (**106**) and (**107**) has been reported. Under the conditions employed the reactions are first order in the thioacetal and the total mercury concentrations.[364-366]

Further studies[367] on the hydrolysis of (**107**) have shown that a reduction in the chloride ion concentration leads to a marked increase in rate. The approximate relative reactivities of the different mercury(II) species in solution are Hg^{II} (1) ≈ $HgCl^+$ (1) ≈ $HgCl_2$ (1) > $HgCl_3^-$ (0.1) ≫ $HgCl_4^{2-}$ (<0.001). The rate constant for reaction *via* Hg^{II} is *ca.* 10^6-fold larger than for hydrolysis in the presence of H_3O^+ alone. Addition of HCl leads to a reduction in rate, rather than an increase, presumably due to the formation of less reactive chloro complexes. Hydrolysis of (**107**)



(106)



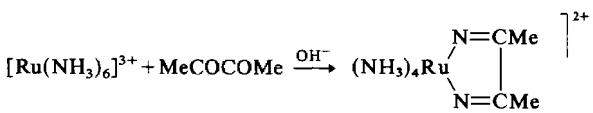
(107)

appears to involve rapid pre-equilibrium formation of a mercury complex with the S-atom of the acetal followed by a slow unimolecular breakdown of the acetal–mercury complex, while hydrolysis of (**106**) proceeds by slow attack of solvent water on the acetal–mercury complex.

Studies of metal ion promotion of the reactions of thiocarboxylic acids and anhydrides,[363] thioamides[368–370] and a variety of other sulfur compounds have been carried out. The interested reader should consult the comprehensive review by Satchell.[17]

61.4.8 FORMATION OF IMINES

Recent studies have shown that coordinated ammonia and amine ligands under basic conditions may effect nucleophilic attack at carbonyl centres in organic compounds.[371–376] These reactions occur due to formation of deprotonated amido species which can act as nucleophiles. For example, reaction of cobalt(III) and platinum(IV)ammines with ketones gives the corresponding Co^{III} and Pt^{IV} imine complexes. A similar reaction between $[Ru(NH_3)_6]^{3+}$ and diones produces the corresponding Ru^{II} diimine (**108**).[377] It has also been found[378] that nitrilepentaammineruthenium(II)



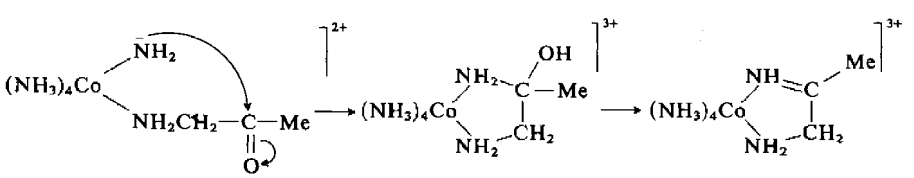
(108)

complexes $[(NH_3)_5RuN{\equiv}CR]^{2+}$ (R = Me or Ph) can be prepared by the reaction of $[Ru(NH_3)_6]^{3+}$ with the appropriate aldehydes (equation 30). This report appears to be the first to describe the formation of a nitrile from the reaction of an aldehyde with a transition metal ammine nucleophile.

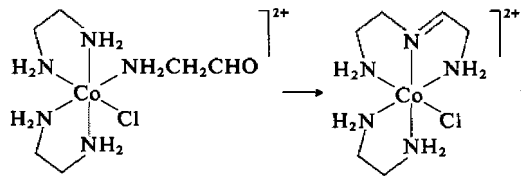
$$[Ru(NH_3)_6]^{3+} + RCHO \xrightarrow{OH^-} [(NH_3)_5RuN{\equiv}CR]^{2+} \qquad (30)$$

A pK_a value of *ca.* 12.4 has been reported[379] for the $[Ru(NH_3)_6]^{3+}$ ion. Solutions of 0.03 M $[Ru(NH_3)_6]Br_3$ containing a 100-fold excess of acetaldehyde or benzaldehyde react rapidly (complete in less than 1 min based on colour change) to produce the nitrile complexes.[378]

A number of intramolecular reactions of this general type have been studied.[380] The $[Co(NH_3)_5(NH_2CH_2COMe)]^{3+}$ ion undergoes intramolecular base-catalyzed cyclization to produce a carbinolamine which undergoes a slower base-catalyzed dehydration to a chelated imine (Scheme 30). The carbonyl group is captured in every other proton exchange. A regio- and stereo-specific intramolecular condensation of aminoacetaldehyde with the deprotonated secondary amine centre *trans* to Cl^- in the *cis*-α-$[Co(trien)(NH_2CH_2CHO)Cl]$ ion has also been shown to occur.[380] A similar type of intramolecular condensation has been observed with *cis*-$[Co(en)_2(NH_2CH_2CHO)Cl]^{2+}$ (**109**),[381] and X-ray crystallography confirms that condensation occurs at an amino group *cis* to Cl^-, giving a product (**110**) in which the tridentate imine ligand adopts a *fac* stereochemistry.

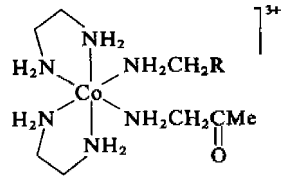


Scheme 30



(109) (110)

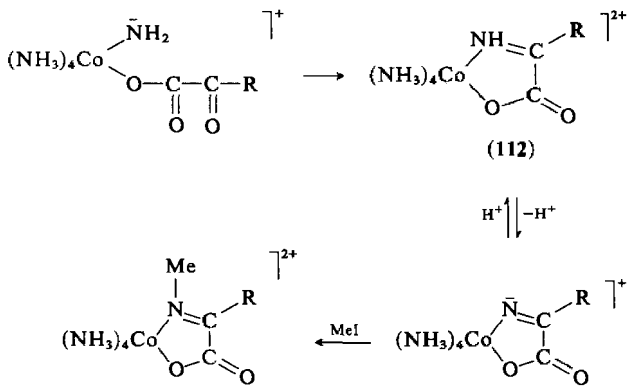
Reactions of this type have possibilities for planned organic and ligand synthesis, as in some cases regio- and stereo-specific condensations have been observed. For example, Gainsford and Sargeson[375] have reported that treatment of (**111**; R = H, Me, CH_2Br, Ph, *p*-C_6H_4Cl) with base leads to imine complexes where the coordinated aminoacetone has reacted with a bound monoamine (RCH_2NH_2) or ethylenediamine moiety. The product distribution appears to be determined by the relative acidity of the monoamine and ethylenediamine NH centres; condensation is preferred at the most acidic site. Reduction of the imine group in these complexes with BH_4^- gives the new complexes $[Co(en)_2(NH_2CH_2CH(Me)NHCH_2R)]^{3+}$ and $[Co(en)(NH_2CH_2CH_2NHCH(Me)CH_2NH_2)(NH_2CH_2R)]^{3+}$ in which the reduced ligand is synthesized stereospecifically.



(111)

Coordinated ligand reactions of this type have been used to synthesize a variety of macrocyclic complexes of the clathrochelate type,[382] and somewhat similar reactions have been used quite generally in the macrocycle field.[383]

Complexes of the type $[Co(NH_3)_5OCOCOR]^{2+}$ (R = H, Me, Ph, CO_2H, CH_2Ph, Bu^t, $CH_2CH_2CO_2^-$) have been prepared.[384] In aqueous base most of these ions undergo cyclization (Scheme 31) to tetraammine iminocarboxylato chelates (**112**) which deprotonate in basic solution. These complexes undergo a variety of reactions; *e.g.* alkylation of the deprotonated imine N centre with reagents such as MeI (Scheme 31) and reduction of the imine to give amino acids. The isolation of imine complexes formed by the condensation of acetaldehyde with Co^{III}-1,2-ethanediamine complexes has also been described.[388] In one case two such acetaldimine moieties condense stereospecifically. Another acetaldimine product derived from Λ-$[Co(en)_2(S\text{-Tyr})]^{2+}$ was also prepared and its crystal structure determined.



(112)

Scheme 31

A number of interesting studies have also been carried out using labile metal ions. The effect of metal ions on the mechanism of the condensation of the salicylaldehydato ion (sal) with primary amines has been studied kinetically.[385-387] Under suitable experimental conditions, the reaction of sal^- with diethylenetriamine (dien) in the presence of copper(II) occurs by first order kinetics.[387] The reaction is envisaged to occur by prior coordination of the reactants to copper,

Table 25 Activation Parameters for the Bimolecular Condensation of sal^- with dien and the Copper(II) Template Condensation[a]

Reaction	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
$Sal^- + dien$	24.6	−159.3
$[Cu(sal)(S)_2]^+ + dien$[b]	48.5	−158.4

[a] Data from E. Rotundo and F. Priolo, *J. Chem. Soc., Dalton Trans.*, 1982, 1825.
[b] S = solvent molecule.

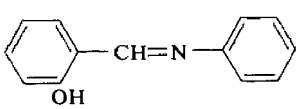
followed by interligand condensation within the ternary complex. Activation parameters have been determined for the bimolecular condensation reaction of sal with dien, and for the copper(II) template condensation (Table 25).

An extensive review on the formation of Schiff bases in the coordination sphere of metal ions is available.[389]

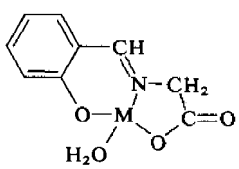
61.4.9 IMINE HYDROLYSIS

The effect of metal ions on the hydrolysis of imines is of considerable biological interest. A number of papers have discussed the effect of metal ions on the formation and hydrolysis of such compounds.[389-400] Until recently detailed kinetic studies on imine hydrolysis were lacking, but a number of detailed investigations have now been carried out. The low solubility of many aromatic imines (which are generally more readily characterized) in aqueous solution has led to the use of mixed alcohol-water solvent systems which can lead to problems of interpretation.

A kinetic study of the hydrolysis of *N*-salicylideneaniline (**113**) in the presence and absence of cobalt(II), nickel(II), copper(II) and zinc(II), using 10% ethanol-water as solvent, has been carried out by Dash and Nanda.[397] The (1:1) Schiff base-metal complexes (ML^+) were found to undergo acid-catalyzed hydrolysis at rates decreasing with the thermodynamic stabilities of the complexes, the most thermodynamically stable complexes undergoing the slowest rate of hydrolysis. More recent measurements[401] using high copper(II) to ligand ratios have indicated that the copper(II)-imine is quite stable to hydrolysis at pH 5.

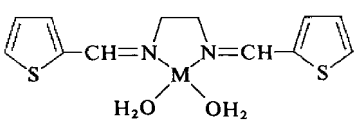


(**113**)

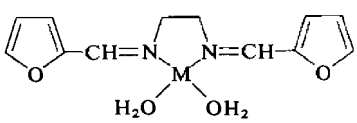


(**114**)

Imines capable of forming bicyclic chelate rings as in (**114**) are known to be stabilized towards hydrolysis under mildly acidic conditions.[392] However, imines which can form monocyclic chelates such as *N,N'*-ethylenebis(2-thienylmethyleneimine) (**115**)[390,391,402,404] and *N,N'*-ethylenebis(2-furanylmethyleneimine) (**116**)[403,405,406] where the S and O atoms respectively do not act as donors are rapidly hydrolyzed in the presence of copper(II) and nickel(II) ions. Hydrolysis of a bicyclic metal complex such as (**114**) involves the rupture of chelate rings, a process which is not normally favoured.



(**115**)



(**116**)

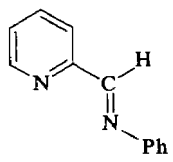
Hay and Nolan[407] have carried out a detailed kinetic study on the hydrolysis of *N*-2-pyridylmethyleneaniline (**117** = L) and its copper(II) complex (**118**). Very substantial rate accelerations were observed in this system. Base hydrolysis of $[CuL(OH_2)_2]^{2+}$ (**118**) is some 10^5 times faster than base hydrolysis of L at 25 °C. The rate constants for this system are summarized in Table 26.

The kinetics of hydrolysis of *N*-salicylidene-2-aminothiazole (**119** = HL) have been studied in aqueous 5% methanol in the presence and absence of Co^{II}, Ni^{II}, Cu^{II} and Zn^{II}.[408] The solvent deuterium isotope effect on the rate of spontaneous and hydroxide-catalyzed hydrolysis of the Schiff-base anion (L^-) is consistent with intramolecular catalysis by the phenoxide ion. Only

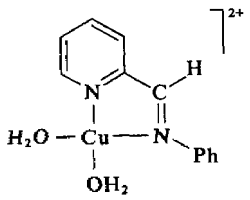
Table 26 Rate Constants for the Hydrolysis of *N*-2-Pyridylmethyleneaniline (L) at 25 °C and $I = 0.1$ M[a]

Reaction	*k*
$HL^+ + H_2O$	$1.26 \times 10^{-1}\ M^{-1}\ s^{-1}$
$L + OH^-$	$2.17 \times 10^{-2}\ M^{-1}\ s^{-1}$
$L + H_2O$[b]	$2.8 \times 10^{-4}\ s^{-1}$
$HL^+ + OH^-$[b]	
$[CuL(OH_2)_2]^{2+} + H_2O$	$3.15 \times 10^{-6}\ M^{-1}\ s^{-1}$
$[CuL(OH_2)_2]^{2+} + OH^-$	$9.72 \times 10^{3}\ M^{-1}\ s^{-1}$
$[CuL(OH)(OH_2)]^{+} + OH^-$	$2.75 \times 10^{3}\ M^{-1}\ s^{-1}$

[a] Data taken from R. W. Hay and K. B. Nolan, *J. Chem. Soc., Dalton Trans.*, 1976, 548.
[b] These reactions are kinetically indistinguishable.

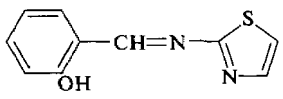


(117)

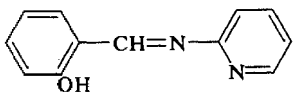


(118)

copper(II) significantly retards the rate of hydrolysis of the imine. This effect is due to the formation of the less reactive $[CuL]^+$ species, although both spontaneous and acid-catalyzed hydrolysis of the imine linkage is still observed in the pH range 4.22–5.2.



(119)



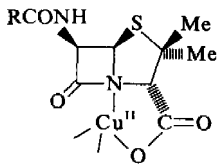
(120)

Hydrolysis of *N*-salicylidene-2-aminopyridine (**120** = HL) in aqueous 5% methanol, in the presence and absence of copper(II), has been the subject of a detailed kinetic study.[409] The imine anion (L^-) is found to undergo hydroxide-independent hydrolysis with $k = 3.5 \times 10^{-2}\ s^{-1}$ at 35 °C. The observed solvent deuterium isotope effect ($k_{H_2O}/k_{D_2O} = 1.6$) for this pathway is consistent with intramolecular catalysis by the phenoxide ion. The copper(II) complex undergoes acid-catalysed hydrolysis of the imine linkage with $k = 4.4 \times 10^{2}\ M^{-1}\ s^{-1}$ at 35 °C.

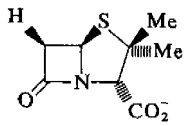
61.4.10 LACTAM HYDROLYSIS: PENICILLINS, CEPHALOSPORINS

A number of interesting studies of lactam hydrolysis have been published. The metal(II)-catalyzed hydrolysis of some penicillin and cephalosporin derivatives displays saturation kinetics.[410–412] A 1:1 complex is formed between the metal ion and penicillin which undergoes base hydrolysis up to 10^8 times faster than the free ligand. The catalytic activity follows the order $Cu^{II} > Zn^{II} > Ni^{II} = Co^{II}$. Coordination of penicillin to copper(II) is believed to occur *via* the β-lactam nitrogen and the carboxylate group (**121**)[410,411] but other sites have been proposed.[413]

Coordination *via* the carboxylate group is consistent with the observation that esterification of this group decreases the rate enhancement by *ca.* 5×10^3. In addition, the IR spectra of copper(II) β-lactam complexes show a decrease in the carboxylate carbonyl stretching frequency of

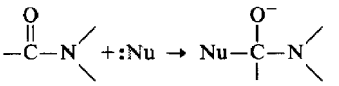


(121)

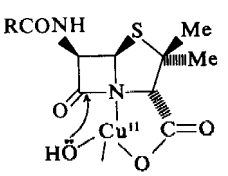


(122)

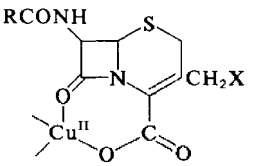
ca. 40 cm^{-1} compared with that of the sodium salt.[411] Previous suggestions[413] that copper(II) binds to the 6-acylamino side chain and the β-lactam carbonyl group appear to be incorrect as complete removal of the amido side chain as in penicillanic acid (**122**) also gives similar binding constants and rate enhancements.[411,414] Page[411] has argued that nucleophilic addition to the β-lactam carbonyl group to give a tetrahedral intermediate causes a large change in the basicity of the β-lactam nitrogen (*ca.* 15 pK units) (equation 31) so that coordination to nitrogen should greatly increase the stability of the intermediate. However, other effects such as intramolecular attack by coordinated hydroxide as in (**123**) could also occur in such systems and such pathways are not excluded by the kinetic data. Details of the copper(II)-catalyzed reactions are summarized in Table 27. In the case of benzylpenicillin the rate enhancements compared with the free ligand are Cu^{II} (8×10^7), Zn^{II} (4×10^5), Ni^{II} (4×10^4) and Co^{II} (3×10^4). The analogous data for cephaloridine are Cu^{II} (3×10^4) and Zn^{II} (2×10^3).[414]



(31)



(**123**)



(**124**)

Table 27 Rate Constants and Formation Constants for the Copper(II)-catalyzed Hydrolysis of β-Lactam Substrates at 30 °C ($I = 0.5$ M)[a]

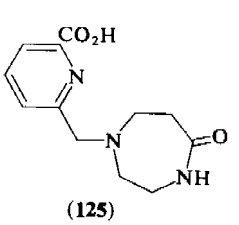
β-Lactam	k_{OH} ($M^{-1}s^{-1}$)	K (M^{-1})	$k_{OH}^{complex}$ ($M^{-1}s^{-1}$)	$k_{OH}^{complex}/k_{OH}$
Benzylpenicillin	0.154	187	1.22×10^7	8×10^7
Benzylpenicillin methyl ester	2.51	—	$<3\times10^4$	$<1.5\times10^4$
6-β-Aminopenicillanic acid	6.35×10^{-2}	232	5.15×10^6	8×10^7
Penicillanic acid	7.40×10^{-3}	120	1.58×10^6	2×10^7
Cephaloridine	0.526	2080	1.64×10^4	3×10^4
3-Methyl-7-β-phenylacetamidoceph-3-4-carboxylic acid	2.41×10^{-2}	2400	1.56×10^3	7×10^4

[a] Data from N. P. Gensmantel, P. Proctor and M. I. Page, *J. Chem. Soc., Perkin Trans. 2,* 1980, 1725.

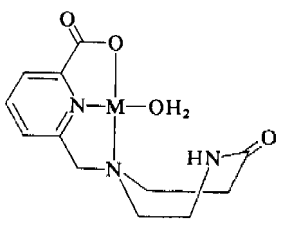
Copper(II) binds some 10-fold more strongly to cephalosporins than to penicillins.[411,414] Molecular models indicate that one of the conformations of cephalosporins would be very suitable for binding *via* the carboxylate group and the β-lactam carbonyl oxygen (**124**) giving rise to a seven-membered chelate ring. Variations in the β-lactam carbonyl stretching frequency on complexation provide some support for structure (**124**).

Bacterial resistance to β-lactam antibiotics is due mainly to enzymic hydrolysis of the β-lactam ring of the antibiotic. Many bacteria produce β-lactamases which hydrolyze both penicillins and cephalosporins to the harmless penicilloic and cephalosporoic acids. It is noteworthy that zinc(II) is an essential cofactor for the β-lactamase II enzyme.[416]

Very rapid hydrolysis of the lactam (**125**) in the presence of copper(II) and zinc(II) occurs.[417,235] The lactam gives 1 : 1 complexes with Cu^{II}, Zn^{II} and Co^{II} which are believed to have the structure (**126**). For the copper(II) complex the pK_a of the coordinated water molecule is *ca.* 7.6. Hydrolysis



(**125**)

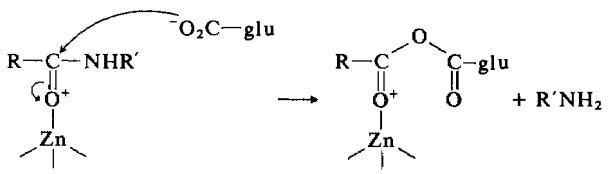


(**126**)

of the copper(II) complex is 1.6×10^6 times faster than that of the free lactam at pH 7.6, while a rate acceleration of 1.9×10^5 occurs with zinc(II). In this case nucleophilic attack by metal-bound hydroxide is considered to be the most plausible pathway for hydrolysis.

61.4.11 HYDROLYSIS OF ANHYDRIDES

One possible mechanism for the hydrolysis of peptides or esters by carboxypeptidase A involves two steps with an anhydride (acyl-enzyme) intermediate.[418] In the first step, the zinc(II) activates the substrate carbonyl group towards nucleophilic attack by a glutamate residue, resulting in the production of a mixed anhydride (**127**). Breakdown of the anhydride intermediate is rate determining with some substrates.[419] An understanding of the chemistry of metal ion effects in anhydride hydrolysis is therefore of fundamental importance in regard to the mechanism of action of the enzyme. Until recently there have been few studies of metal ion-catalysed anhydride solvolysis.



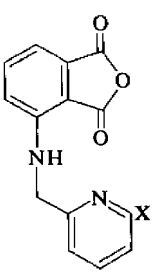
(**127**)

Breslow and coworkers[420] have studied the hydrolysis of the anhydrides (**128**) and (**129**) in both the presence and absence of zinc(II) (and other metal ions). In the the absence of metal ion, hydrolysis of the anhydrides is independent of pH in the region 1.0–7.5, as also occurs with phthalic anhydride.[421] However, in the presence of zinc(II), the hydrolysis is first order in hydroxide above pH 5. Table 28 lists values of k_{obs} for the various substrates at pH 7.5 (for the metal complex $k_{obs} = k_{OH}[OH^-]$). The catalytic effects are of the order of 10^3. The pH dependence of the zinc(II) catalysis is consistent with attack by external hydroxide on a complex such as (**130**) where the metal acts as a Lewis acid catalyst. A further possibility involves attack by coordinated hydroxide on an uncoordinated anhydride carbonyl (**131**), and there is some evidence that this is indeed the process which does occur.

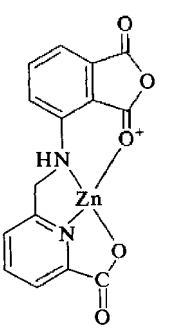
Table 28 Observed First Order Rate Constants for the Hydrolysis of the Anhydrides (**128**) and (**129**) and their Metal Complexes at pH 7.50[a]

Substrate	k_{obs} (s^{-1})	k_{rel}
(**128**)	2.7×10^{-3}	1.0
(**128**) + Zn^{2+}	3.0	10^3
(**129**)	5.5×10^{-3}	2.0
(**129**) + Zn^{2+}	1.5	5×10^2

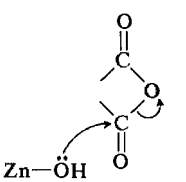
[a] Data from R. Breslow, D. E. McClure, R. S. Brown and J. Eisenach, *J. Am. Chem. Soc.*, 1975, **97**, 194



(**128**) X = CO_2H
(**129**) X = H

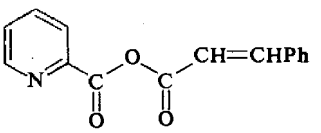


(**130**)

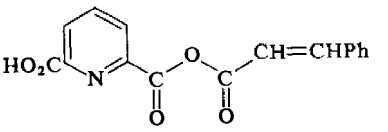


(**131**)

Rate constants have also been determined for the hydrolysis of cinnamic picolinic anhydride (**132**) and cinnamic 6-carboxypicolinic monoanhydride (**133**) in 50% dioxane-H_2O at 30 °C.[422]



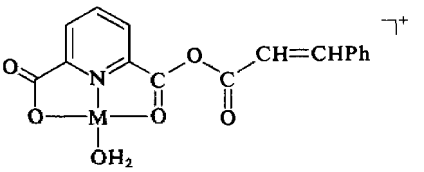
(132)



(133)

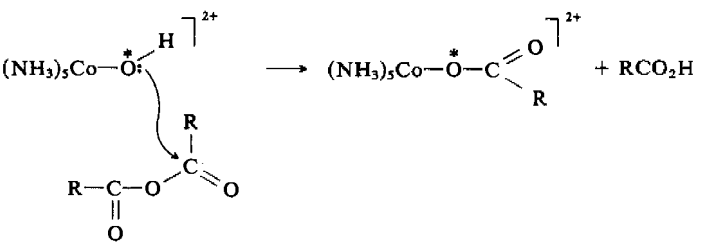
Divalent metal ions (Cu^{II}, Ni^{II}, Co^{II} and Zn^{II}) have a significant catalytic effect in the hydrolysis of (**132**), although only limited complexation occurs and saturation effects were not observed. Rate enhancements ranged from 200-fold with 5×10^{-4} M Cu^{II} to 10-fold with 5×10^{-3} M Zn^{II}. The reactions at constant metal ion concentration are pH independent indicating water attack on the complex.

Metal ion binding to (**133**) is quite strong and saturation kinetics occur at low metal ion concentrations presumably leading to complexes of type (**134**). Base hydrolysis of the Cu^{II} complex is observed, but attack by both H_2O and OH^- occurs with the Ni^{II}, Co^{II} and Zn^{II} complexes. Rate enhancements of $>10^2$ occur for water attack.



(134)

Buckingham and Engelhardt[200] have studied the hydrolysis of propionic anhydride in the presence of kinetically inert complexes of the type $[M(NH_3)_5OH]^{n+}$. These reactions occur by nucleophilic attack of coordinated hydroxide on the anhydride (Scheme 32). For reactions of $M-OH^{(n-1)+}$ with propionic anhydride, the Bronsted plot of log k_{MOH} *versus* the pK_a of $M-OH_2^{n+}$ is a smooth curve if values for reaction with H_2O and OH^- are included. Although k_{MOH} for $[(NH_3)_5CoOH]^{2+}$ ($3\ M^{-1}s^{-1}$) is about 10^3-fold less than k_{OH}, its reaction will compete favourably at neutral pH with base hydrolysis. Such effects are considered in more detail in Section 61.4.2.2.3.

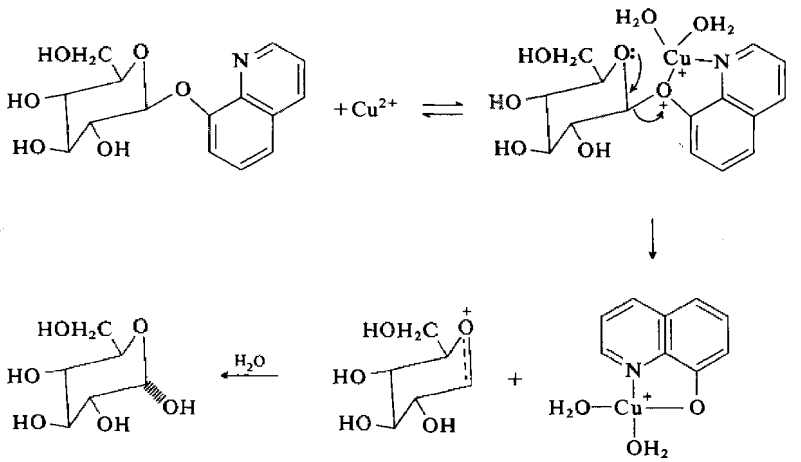


Scheme 32

61.4.12 HYDROLYSIS OF GLYCOSIDES, ACETALS AND THIOACETALS

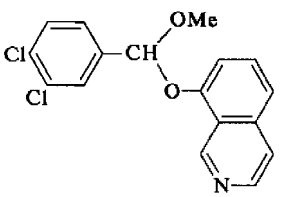
The hydrolysis of glycosides is susceptible to both general and specific acid catalysis,[423,424] and thus cleavage of the glycosidic bond would also be expected to be subject to metal ion catalysis. Simple O-acetals are weak bases and even highly charged ions such as iron(III) have limited effects on their rates of hydrolysis.[425] The use of chelating ligands leads to quite significant effects. Thus Clark and Hay[426] have found that the hydrolysis of 8-quinolyl β-D-glucopyranoside is subject to pronounced catalysis by copper(II) (8-hydroxyquinoline was chosen as the aglycone in order to provide a binding site for the metal ion close to the glucosidic bond). Copper(II), nickel(II) and cobalt(II) catalyze the reaction but saturation kinetics were not observed. Copper(II) is a particularly effective catalyst and it is estimated that the copper(II) complex is hydrolyzed *ca.* 10^5–10^6 times faster than the uncomplexed glycoside in the pH range 5.5–6.2. The reaction is presumed to occur as shown in Scheme 33.

Przystas and Fife[427] have studied the hydrolysis of substituted benzaldehyde methyl 8-quinolyl acetals such as (**135**) in 50% dioxane-water at 30 °C. These acetals are subject to both general and specific acid catalysis. A variety of divalent metal ions (Cu^{II}, Co^{II}, Ni^{II}, Mn^{II} and Zn^{II}) exert

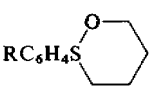


Scheme 33 Metal ion-catalyzed hydrolysis of 8-quinolyl β-D-glucopyranoside

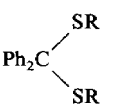
a large catalytic effect even though complexation is quite weak. For example, a 0.02 M concentration of Ni^{II} (1000-fold excess over the substrate) at pH 7.2 leads to a 2×10^5-fold increase in k_{obs} for the hydrolysis of (**135**). Metal ion catalysis is attributed to a transition state effect in which the leaving group is stabilized.



(**135**)



(**136**)



(**137**)

S-Acetals are very readily hydrolyzed in the presence of soft metal ions and large rate accelerations (*e.g. ca.* 10^6-fold compared with the proton) are found. In the case of S-acetals such as (**136**) only a small extent of pre-equilibrium complex formation occurs[428] even with Hg^{II}, but for substrates such as (**137**), 1:1 complex formation readily occurs with weaker binding metal ions such as Ag^I. Kinetic terms reflecting binding of two Ag^I ions to the substrate (**137**) are detectable.[429] Both A1 and A2-like schemes have been proposed for these S-acetal reactions and the topic was reviewed[17] in 1977.

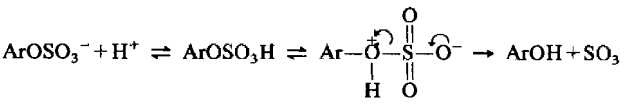
Use can also be made of some of the effects described above for the synthesis of glycosides. Thus phenyl 1-thio-D-glucopyranosides in the presence of mercury(II) salts are readily solvolyzed to give alkyl D-glucopyranosides with inverted anomeric configuration.[430] Methanolysis of the β- and α-anomers gave the methyl α- and β-glycosides which were isolated in yields of 74 and 87% respectively. The approach was extended to the synthesis of complex glycosides (the α-anomers of which are of special interest) by the preparation of cholestanyl and 1-naphthyl α-D-glucopyranosides and a disaccharide derivative.

A number of other reactions in this general area such as the mutarotation of D-(+)-glucose[431,432] and aldose–ketose isomerizations[433] are also subject to catalysis by metal ions.

61.4.13 HYDROLYSIS OF SULFATE ESTERS

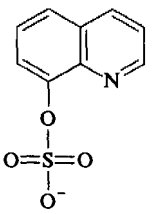
Although metal-promoted hydrolysis of phosphate esters is a topic of very current interest (Section 61.4.4), little work has been published dealing with the effects of metal ions on the hydrolysis of sulfate esters. The acid-catalyzed hydrolysis of aryl sulfates has been shown to occur by an A-1 mechanism (Scheme 34).[434] Nucleophilic catalysis by amines has been observed in the hydrolysis of *p*-nitrophenyl sulfate[435] and intramolecular carboxyl group catalysis occurs with salicyl sulfate[436] as with salicyl phosphate.

The hydrolysis of 8-quinolyl sulfate (**138**) is strongly promoted by copper(II) in the pH range 5.4–5.8 at 39.8 °C.[437] The 1:1 copper(II) complex which is believed to have the structure (**139**)

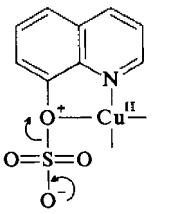


Scheme 34

hydrolyzes 10^5-10^6 times more rapidly than the free ligand in the pH range 5–6. Further investigations of the effect of metal ions on sulfate ester hydrolysis are required. Most aryl sulfatases have pH optima in the acidic range (pH 4–6), but currently there appears to be no evidence for any metal-activated aryl sulfatase enzyme.



(138)



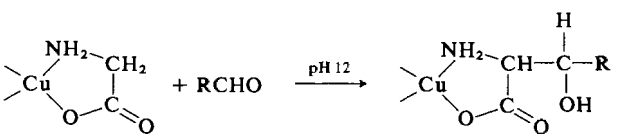
(139)

61.4.14 REACTIONS OF COORDINATED AMINO ACIDS

The various reactions undergone by coordinated amino acids have been the subject of several reviews[28,31,32,438,446] and only a brief discussion will be given here. The reactions which occur can be roughly classified under three headings: (a) aldol condensations, (b) reactions of complexes of amino acid Schiff bases, and (c) isotopic exchange and racemization at the α-carbon of the amino acid.

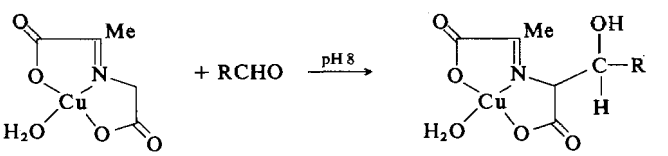
61.4.14.1 Aldol Condensations

The synthetic applications of these reactions are considered in Section 61.4.15. Reaction of copper(II) glycinate with formaldehyde in aqueous solution at pH 12 gives serine, while reaction with acetaldehyde gives a mixture of threonine and allothreonine (Scheme 35). This reaction has been extended to a variety of aldehydes to obtain longer chain β-hydroxyamino acids.[439]



Scheme 35

Similar reactions are undergone by Schiff base derivatives. Thus the Schiff base formed between pyruvic acid and glycine undergoes a similar reaction under weakly basic conditions (Scheme 36).[440]



Scheme 36

Schiff base complexes such as *N*-salicylideneglycinatoaquacopper(II) will also react with alkyl halides under basic conditions giving the alanine derivative (with MeI) and phenylalanine with benzyl bromide.[441]

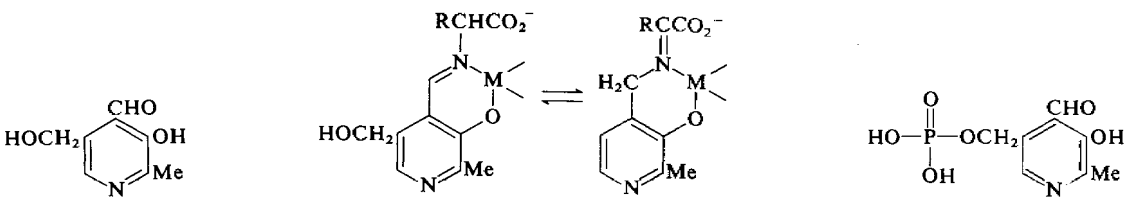
The synthesis of threonine can be made stereospecific using optically active complexes of the type L-$[Co(en)_2Gly]^{2+}$ but with low asymmetric yield.[442] In the case of dipeptide complexes only

the C-terminal residue is activated,[443] thus in the reaction between $[Co(dien)(GlyGly)]^+$ and acetaldehyde at pH *ca.* 11, the product is $[Co(dien)(GlyThr)]^+$.

61.4.14.2 Schiff Bases

Schiff base formation can have a considerable effect on both the position and degree of activation of the coordinated amino acid. The Schiff bases derived from amino acids and pyridoxal have attracted considerable attention due to the biochemical significance of vitamin B_6 and the realization that many of the enzymic reactions involving B_6 could be brought about in the absence of enzyme by using pyridoxal and various metal ions.[444,445,461,462,542]

Schiff base formation between pyridoxal (**140**) and amino acids leads to complexes of type (**141**) which are in tautomeric equilibrium with (**142**). This tautomeric equilibrium leads to transamination, thus the same metal complexes can be obtained when either pyridoxal and alanine or pyridoxamine and pyruvic acid are allowed to react together in the presence of a metal ion. Hopgood[447] has studied the rates of transamination of 15 amino acids in the presence of zinc(II) and pyridoxal 5-phosphate (**143**). On mixing the reagents zinc(II)-aldimine complexes are rapidly formed (*ca.* 5 min) and these species subsequently transaminate in a slow second step. Al^{III} and Zn^{II} systems have been particularly well studied.[448–450] The role of the metal ion seems to involve both stabilization or 'trapping' of the Schiff base, and in addition it also ensures the planarity of the conjugated π-system. In the case of the aldimine tautomer, extensive ^1H NMR studies[448,450] have shown that formation of the ternary complex results in activation at the amino acid 2-carbon. At room temperature the reaction occurs without incorporation of ^2H into the aldehyde methine position indicating that the primary mechanism is carbanion formation rather than tautomerism.



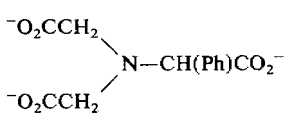
(**140**) (**141**) (**142**) (**143**)

61.4.14.3 Isotopic Exchange and Racemization

The activation of the normally inert methylene group of glycine by coordination to a transition ion has been recognized for many years. The substantial increase in the acidity of the methylene hydrogens has been directly confirmed by deuterium labelling experiments,[451] and has also been shown to occur in other α-aminocarboxylate complexes of cobalt(III)[451–456] and platinum(II).[457]

Norman and Phipps[458] carried out a systematic investigation of the effect of various metal ions on the activation of the methylene protons of EDTA using ^1H NMR techniques. Of the 30 metal ions studied only seven, all transition metal ions VO^{II}, Cr^{III}, Fe^{II}, Co^{II}, Co^{III}, Rh^{III}, Ni^{II}, Cu^{II}, enhanced the activation of the methylene groups of the ligand. A true catalytic effect was observed with Ni^{II} which induced complete exchange even in the presence of a large excess of the ligand.

Stadherr and Angelici[459] studied the effects of various metal ions on the base-catalyzed racemization and deuterium exchange at the methine hydrogen of *N,N*-bis(carboxymethyl)-D-phenylglycine (**144**). The metal complexes underwent racemization at rates up to 5×10^3 times greater than for the free ligand.



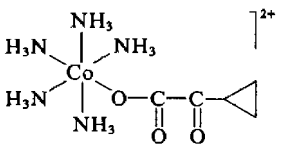
(**144**)

A recent paper[460] has questioned some of the above results and reports that Ni^{II} when complexed to L-alanine and Co^{III} when complexed to Gly-Ala or Ala-Gly *retard* the rate of racemization of the L-alanine. A detailed study of the pH rate profile on free and Ni^{II}-complexed L-alanine indicated that above pH 4 the free amino acid racemized faster than the complex. Further studies of these reactions are required.

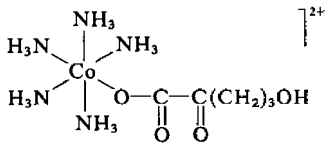
61.4.15 AMINO ACID SYNTHESIS AND ALDOL CONDENSATIONS

Coordinated ligand reactions have been used to synthesize a variety of amino acids, and some of the approaches employed are discussed below.

Intramolecular imine formation between a coordinated aminate ion and a 2-oxo acid has been utilized to synthesize the two racemic amino acids 2-cyclopropylglycine and proline.[463] Thus anation of $[Co(NH_3)_5OH_2]^{3+}$ by $Br(CH_2)_3COCO_2H$ at pH 5 gives two major products (**145**) and (**146**). Both are converted to tetraammineiminocarboxylato chelates by attack of an adjacent deprotonated ammonia. The cyclopropylimine complex can, for example, be reduced by alkaline BH_4^- to give the (*RS*)-2-cyclopropylglycine complex.

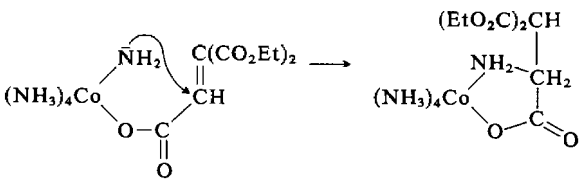


(**145**)



(**146**)

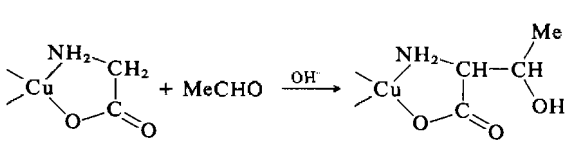
The cobalt(III)-promoted synthesis of β-carboxyaspartic acid has also been reported[464] by the intramolecular addition of coordinated aminate ion to the alkenic centre in the (3,3-bis(ethoxycarbonyl)-2-propenoato)pentaamminecobalt(III) ion $[(H_3N)_5CoOOCCH{=}C(CO_2Et)_2]^{2+}$. In aqueous solution, an intramolecular addition of the *cis*-aminate ion at the alkenic centre gives the *N,O*-chelated diester of β-carboxyaspartic acid (Scheme 37).



Scheme 37

Coordination of α-amino acids to metal ions has long been known to increase the acidity of the C—H bond at the α-carbon atom and various reviews of the topic are available.[31,32]

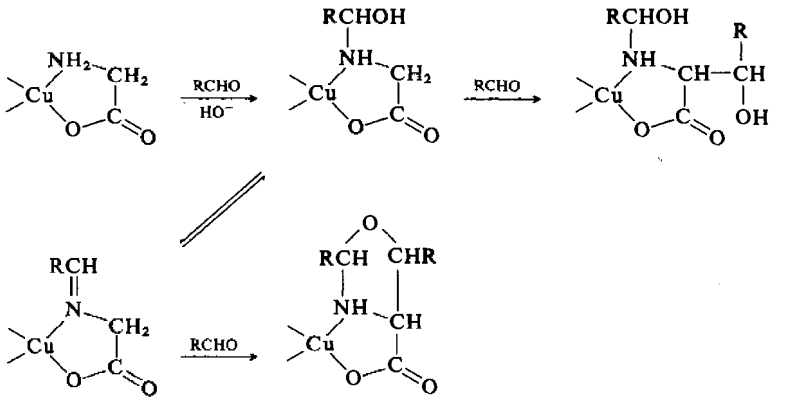
The original observation[465] that copper(II) ions promote the base-catalyzed condensation of acetaldehyde with glycine to give threonine (**147**) was rapidly followed by a number of reports of similar reactions.[466,467] Since this early work a great deal of literature has appeared concerning the reaction of metal complexes of amino acids[468–472] or small peptides[473,474] with various aldehydes. The reaction has also been carried out using chiral octahedral cobalt(III) complexes containing glycine with relatively high asymmetric yields but low overall yields.[475–477] It was later discovered that the use of an amino acid Schiff base complex instead of an amino acid metal complex increased the acidity of the C—H bond at the α-carbon atom of the amino acid and also prevented the occurrence of *N*-alkylation.[478–481] Thus the glycine residue in *N*-salicylideneglycyl-L-valinatocopper(II) reacts with formaldehyde in aqueous solution at pH 8.5. Decomposition of the complex with H_2S at pH 2 gives seryl-L-valine containing optically active serine.[482]



(**147**)

In the case of copper(II) complexes, the reaction with acetaldehyde is believed to proceed by the steps shown in Scheme 38. The bis(oxazolidine)copper(II) complex (**148**; R = Me) has been characterized by X-ray analysis.[486] Treatment of this complex with H_2S in acid solution gives threonine. Synthetic procedures have been developed giving threonine in 95% yields.[483]

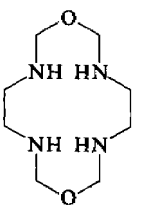
The condensation of formaldehyde with glycine or glycine Schiff bases coordinated to Co^{III}, Cu^{II} and Ni^{II} has been shown to give α-hydroxymethylserine.[484] With $[Cu(GlyO)_2]$ the reaction of formaldehyde at the α-carbon is preceded by condensation on the amino group and is followed by cyclization to give an oxazolidine-type ring.



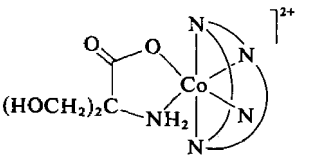
(148)

Scheme 38

Condensation of formaldehyde with $[Co(en)_2(GlyO)]^{2+}$ gives as the initial product α-hydroxymethylserinebis(ethylenediamine)cobalt(III) which is subsequently converted into the α-hydroxymethylserine-1,4,8,11-tetraaza-6,13-dioxacyclotetradecanecobalt(III) ion containing the macrocyclic ligand (**149**) which is coordinated *via* the nitrogen donors as in (**150**).[485] Cooke and Dabrowiak[476] have studied the reaction of acetaldehyde with optically active $[Co(en)_2(GlyO)]^{2+}$. The isolated threonine and allothreonine contain an excess of the *S*-enantiomer indicating that the aldehyde prefers to attack the *S* 'side' of the coordinated glycine.



(149)

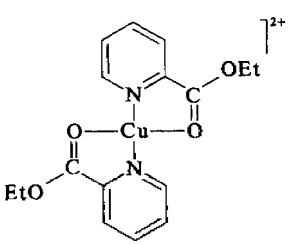


(150)

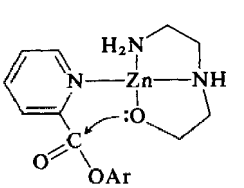
61.4.16 ESTER EXCHANGE REACTIONS

A number of metal complexes of carboxylic esters undergo transesterification on refluxing with alcohols.[487,488] Thus copper(II) complexes of ethyl picolinate (**151**) on refluxing in methanol give the analogous complexes of methyl picolinate.[488] In some cases methanolysis rather than transesterification occurs, as with bis(ethyl acetoacetato)copper(II) which gives methoxy-bridged derivatives in refluxing methanol.[489]

Sigman and Jorgenson[490] have found that zinc(II) catalyzes the transesterification reaction between *N*-(β-hydroxyethyl)ethylenediamine and 4-nitrophenyl picolinate. This reaction involves a reactive mixed ligand complex (**152**) in which the zinc(II) ion perturbs the pK_a of the hydroxyethyl group of *N*-(β-hydroxyethyl)ethylenediamine to provide a high effective concentration of the nucleophile. Intramolecular nucleophlic attack then occurs at the carbonyl group of *p*-nitrophenyl picolinate. This system provides a somewhat unique example of intramolecular



(151)



(152)

attack by a coordinated nucleophile in a labile complex, the reaction pathway being confirmed by the nature of the products obtained.

The complex bis(pentane-2,4-dionato)-μ,μ'-dimethoxy-dicopper(II) has been found to be a very effective and selective catalyst for ester exchange of both 2-ethoxycarbonylpyridine and ethyl 2-pyridylacetate to give the corresponding methyl esters.[491]

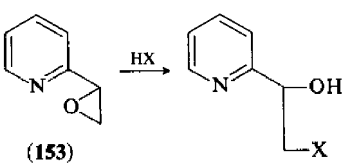
A number of studies have been carried out on the ligand reactivities of the metal complexes of Schiff bases derived from amino acid esters and carbonyl compounds. Ester exchange reactions were first reported by Pfeiffer *et al.*[492] and extended by other investigators.[493–496]

Copper(II) complexes of the Schiff bases derived for salicylaldehyde and dibenzyl asparate or glutamate have recently been characterized.[497] Refluxing these complexes in methanol for 30 min gives bis(α-methyl-β-benzyl-*N*-salicylideneaspartato)copper(II) in which selective ester and bis(α-methyl-γ-benzyl-*N*-salicylideneglutamato)copper(II) exchange occurs. A similar selective ester exchange reaction has also been observed with the copper(II) complex of the Schiff base derived from salicylaldehyde and dibenzyl DL-asparate.[498]

61.4.17 HYDROLYSIS OF EPOXIDES

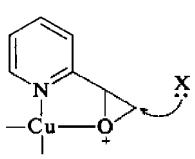
Some interesting work has been published dealing with the metal ion-promoted hydrolysis of epoxides. Hanzlik and Michaely[499] first observed that in the presence of copper(II) the hydration of 2-pyridyloxirane (**153**) is accelerated by a factor of 1.8×10^4 and its reaction with Cl^-, Br^- and MeO^- becomes 100% regiospecific for β-attack. The magnitude of the catalytic effect decreases in the order $Cu^{II} > Co^{II} > Zn^{II} \gg Mn^{II}$. The pH rate profile for the copper(II)-catalyzed reaction is a bell-shaped curve with a maximum at *ca.* pH 5.

Further investigations of the reaction suggest that the bidentate complex (**154**) is the reactive species which undergoes external attack by water or other nucleophiles present in solution. The enzymic hydration of epoxides and the possible role of metal ions has been discussed;[501] the results obtained suggest that a metal ion is not involved at the active site of epoxide hydrase.



(**153**)

X = OH, OMe, Cl, Br

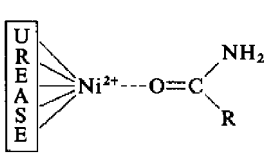


(**154**)

61.4.18 UREA HYDROLYSIS

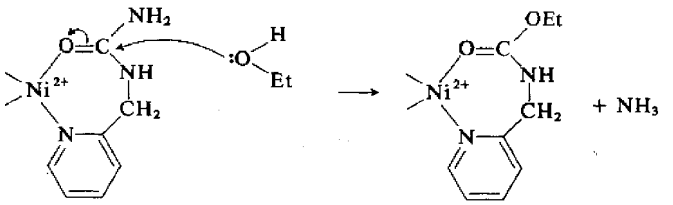
The enzyme urease catalyzes the hydrolysis of urea to form carbamate ion (equation 32). At pH 7.0 and 38 °C, the urease-catalyzed hydrolysis of urea is at least 10^{14} times as fast as the spontaneous hydrolysis of urea. Jack bean urease is a nickel(II) metalloenzyme[502] with each of its six identical subunits containing one active site and two metal ions, and at least one of these nickel ions is implicated in the hydrolysis. It has been suggested[503] that all substrates for urease (urea, *N*-hydroxyurea, *N*-methylurea, semicarbazide formamide and acetamide) are activated towards nucleophilic attack on carbon as a result of O-coordination to the active nickel(II) site as in (**155**). Nickel(II) ions have been found[504] to promote the ethanolysis and hydrolysis of *N*-(2-pyridylmethyl)urea (Scheme 39) and this system is considered to be a useful model for the enzyme.

$$H_2NCNH_2 + H_2O \rightarrow H_2NCO_2^- + NH_4^+ \qquad (32)$$



(**155**)

R = NH_2, NHOH, NHMe, $NHNH_2$, H, Me

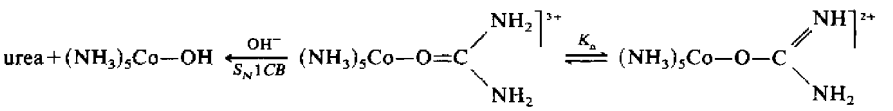


Scheme 39

The synthesis of both O- and N-bonded linkage isomers of the $[Rh(NH_3)_5(urea)]^{3+}$ complexes has been described[505] and their reactions studied in detail. The formation of $[Rh(NH_3)_6]^{3+}$ from $[Rh(NH_3)_5(NH_2CONH_2)]^{3+}$ represents the first observation of non-enzymatic enhancement of the decomposition of urea at low pH. Comparison of the rate constant ($k = 2.0 \times 10^{-5}\ s^{-1}$) with that observed for the slow decomposition of urea at low pH (equation 33; $k = 6 \times 10^{-10}\ s^{-1}$ at 25 °C) indicates that coordination to the metal centre increases the reactivity by some 3×10^4-fold.

$$NH_2CONH_2 \rightarrow NH_3 + HNCO \rightleftharpoons NH_4^+ + NCO^- \qquad (33)$$

The reactions of the pentaamminecobalt(III) complex of urea (O-coordinated) have also been studied.[506] Under basic conditions $[Co(NH_3)_5OH]^{2+}$ is the only cobalt(III) product. The main reaction pathway (*ca.* 97%) is S_N1CB displacement of coordinated urea (Scheme 40) with $k_{OH} = 15.3\ M^{-1}\ s^{-1}$ at 25 °C. A limiting rate was approached at high pH as the complex dissociated to its inactive conjugate base. Hydrolysis of coordinated urea was not observed.



Scheme 40

The complexes $[Cr(NH_3)_5L]^{3+}$ (L = $OCHNH_2$, $OC(NH_2)_2$ and $OC(NHMe_2)$] have been characterized as the O-bound isomers.[507] At 25 °C in aqueous base they isomerize to the deprotonated N-bound isomers without competitive hydrolysis. Reacidification regenerates the O-bound isomer rapidly and completely.

The urea pentaammine complexes of Co^{III}, Rh^{III} and Cr^{III} do not provide any evidence for detectable production of $[(NH_3)_5M{-}OOCNH_2]$ required for reactions to model the chemistry of urease. This is not altogether surprising as there is little apparent activation upon coordination. The pK_a of the free ligand (*ca.* 14) is not lowered substantially on Co^{III} (13.19), Rh^{III} (13.67) or Cr^{III} (13.50), and free urea is hydrolyzed slowly in base. Studies with the inert metal centres suggest that coordination through oxygen alone does not activate urea towards hydrolysis. This result suggests that coordination of urea to a single Ni^{II} at the active site of urease is insufficient for catalysis and that a mechanism involving the two metal ions at the active site may be required.

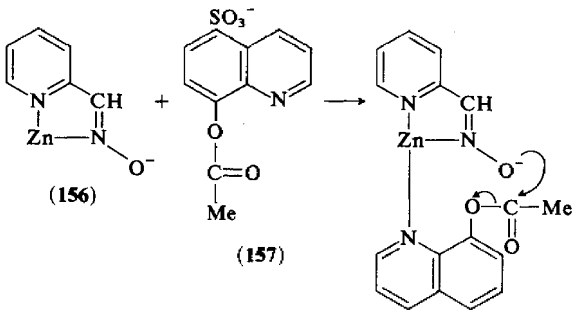
61.4.19 ACYL TRANSFER REACTIONS

One particularly interesting area which has not been subjected to detailed study is metal-promoted acyl transfer. Studies on esterases and peptidases have shown that acyl transfer occurs to a nucleophilic group of the enzyme within an enzyme-substrate complex and the acyl group is then hydrolyzed in the second step. Many of these enzymes, *e.g.* carboxypeptidase, contain zinc(II).

Breslow and Chipman[508] have shown that zinc(II) pyridinecarboxaldimine anion (**156**) provides a strong free nucleophile and is a particularly effective nucleophilic catalyst in the hydrolysis of 8-acetoxyquinoline 5-sulfonate (**157**; Scheme 41).

The reaction involves the catalyst-substrate complex (**158**). Molecular models show that in the mixed ligand complex (**158**), the $N{-}O^-$ group is in a position to attack the acetyl group of (**157**). The zinc complex (**156**) is also an excellent catalyst for the hydrolysis of *p*-nitrophenyl acetate; in fact it is comparable in reactivity to hydroxide ion, although its pK_a is only 6.5, (Table 29).

The hydrolysis of 8-acetoxyquinoline (**159**) is subject to catalysis by metal ions and detailed kinetic studies of the reaction have been reported.[509] The metal ion could be bound to the carbonyl oxygen (**160**) or the ether oxygen (**161**) and the actual structure of the catalytically active complex was not unequivocally defined.



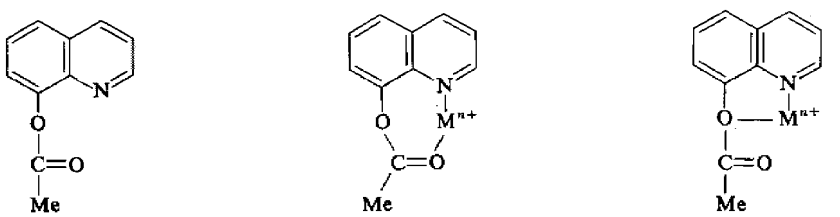
(156) (157) (158)

Scheme 41

Table 29 Rate Constants for Nucleophilic Attack[a,b]

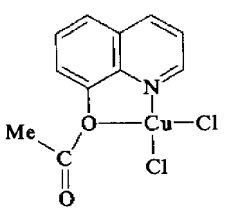
Nucleophile	pK_a	k ($M^{-1}\,s^{-1}$)[c] AQS	PNA
OH^-	15.7	2.01	14.8
PCA anion	10.04	6.98	77.2
H_2O	−1.7	7.3×10^{-7}	1.0×10^{-8}
PCA-Zn^{II}	6.5	10	10

[a] Data from R. Breslow and D. Chipman, *J. Am. Chem. Soc.*, 1965, **87**, 4195.
[b] PCA = pyridine-2-carboxaldoxime, AQS = 8-acetoxyquinoline-5-sulfonate, PNA = *p*-nitrophenyl acetate.
[c] At 25 °C.



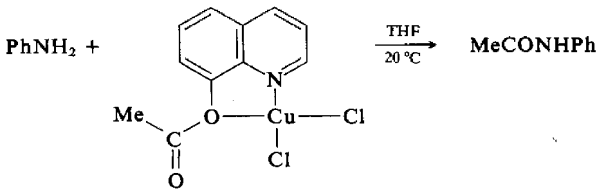
(159) (160) (161)

Sakan and Mori[510] have shown that 8-acetoxyquinoline reacts with copper(II) chloride in dry tetrahydrofuran to give the green complex (**162**). The IR spectrum of the complex has ν(CO) at 1790 cm^{-1} consistent with the ether oxygen acting as a donor. Chelation *via* the carbonyl oxygen would lead to a substantial decrease in the carbonyl stretching frequency (the value of ν(CO) for the free ligand is 1750 cm^{-1}). In (**162**) the carbonyl oxygen is very reactive to nucleophiles owing to polarization of the C—O bond and the substantial thermodynamic stability of the copper(II) complex of 8-hydroxyquinoline (*i.e.* complexation of the leaving group).

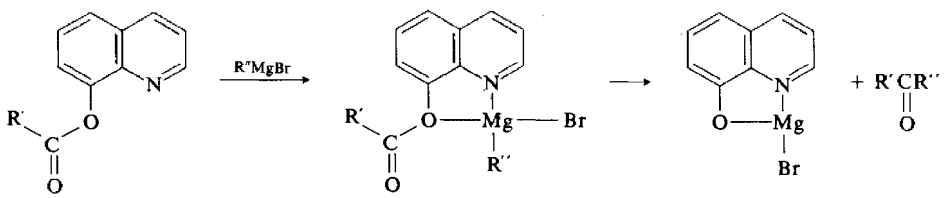


(162)

The complex (**162**) can be used as an acylating agent for alcohols, phenols and amines in THF or benzene solvent (Scheme 42). Acetanilide can be isolated in 83% yield after 2 days at room temperature. In addition 8-acetoxyquinoline will react with Grignard reagents to give high yields (80%) of ketones. The reaction is believed to proceed *via* the intermediate magnesium(II) complex (**163**) (Scheme 43).



Scheme 42



(163)

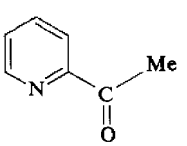
Scheme 43

Some kinetic work on the reaction of Bu^nNH_2 with the copper(II) complex of 8-acetoxyquinoline at 25 °C in DMF as solvent has been carried out. The second order rate constant is $9.5 \times 10^{-2}\ M^{-1}\ s^{-1}$.[511]

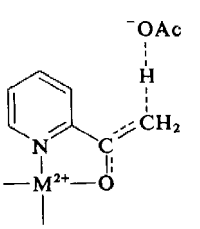
61.4.20 ENOLIZATION

The rates of enolization or ionization of certain keto acids in which the carboxylic group is suitably placed to assist the ionization by interaction with the carbonyl oxygen have been found to be considerably higher (factors of up to 2×10^3) than those of the corresponding keto esters.[512,513] If the carbonyl oxygen can be coordinated to a metal ion, a considerable enhancement of the rate of ionization of the active C—H bond would be expected. Pedersen first observed such a rate enhancement for the acetate-catalyzed halogenation of both ethyl acetate[514] and ethyl 2-oxocyclopentanecarboxylate[515] in the presence of Cu^{II}. The effects were not large presumably due to only weak complexation between Cu^{II} and the ketones.

Complex formation between 2-acetylpyridine (**164** = I) and Zn^{II}, Ni^{II} and Cu^{II} leads to large increases in the rates of enolization or ionization of the C—H bond adjacent to the carbonyl group,[516] the catalytic constants for the acetate-catalyzed iodination being 5×10^3 (ZnL^{2+}) and 2×10^5 (CuL^{2+}) times larger than that of the uncomplexed substrate. This effect, which is considerably larger than that observed on protonation of 2-acetylpyridine (*ca.* 200-fold rate increase), is consistent with stabilization of the negative charge developing on the carbonyl oxygen during ionization of the C—H bond as shown for the transition state (**165**).



(164)



(165)

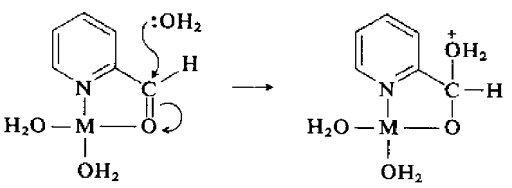
Somewhat similar effects have been observed with acetonyl phosphonate ($MeCOCH_2PO_3^{2-}$).[517,518] The rate of deuteration at the 2-position is some 2000 times faster in the presence of magnesium(II) compared with the free substrate.

Covey and Leussing[339,357] have studied keto–enol tautomerism rates for oxaloacetate ($oxac^{2-}$) and zinc(II) oxaloacetate complexes in acetate buffer solutions at 25 °C. Thus for the equilibrium $oxac_{keto}^{2-} \rightleftharpoons oxac_{enol}^{2-}$ the value of k_f, the rate constant for the forward reaction, for the reaction $oxac_{keto}^{2-} + OAc^-$ is $6.6 \times 10^{-3}\ M^{-1}\ s^{-1}$ while for $Zn(oxac)_{keto} + OAc^-$, k_f is $25\ M^{-1}\ s^{-1}$. The rate

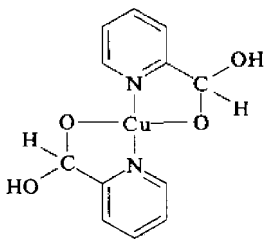
acceleration at 25 °C is *ca.* 4×10^3, very similar to that of 5×10^3 which occurs in the zinc(II)-promoted acetate-catalyzed enolization of 2-acetylpyridine.[516]

61.4.21 CARBONYL GROUP HYDRATION

Carbonic anhydrase is a zinc(II) metalloenzyme which catalyzes the hydration and dehydration of carbon dioxide, $CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$.[525] As a result there has been considerable interest in the metal ion-promoted hydration of carbonyl substrates as potential model systems for the enzyme. For example, Pocker and Meany[519] studied the reversible hydration of 2- and 4-pyridinecarbaldehyde by carbonic anhydrase, zinc(II), cobalt(II), H_2O and OH^-. The catalytic efficiency of bovine carbonic anhydrase is *ca.* 10^8 times greater than that of water for hydration of both 2- and 4-pyridinecarbaldehydes. Zinc(II) and cobalt(II) are *ca.* 10^7 times more effective than water for the hydration of 2-pyridinecarbaldehyde, but are much less effective with 4-pyridinecarbaldehyde. Presumably in the case of 2-pyridinecarbaldehyde complexes of type (**166**) are formed in solution. Polarization of the carbonyl group by the metal ion assists nucleophilic attack by water or hydroxide ion. Further studies of this reaction have been made,[520,521] but the mechanistic details of the catalysis are unclear. Metal-bound nucleophiles (M—OH or M—OH_2) could, for example, be involved in the catalysis.



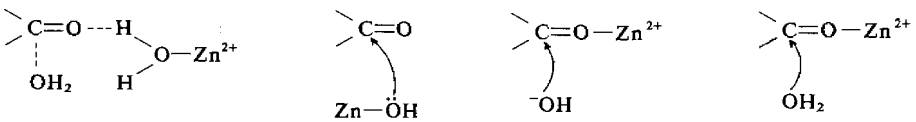
(**166**)



(**167**)

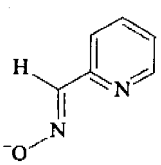
The interaction of 2-pyridinecarbaldehyde with Cu(II) has been studied by potentiometric and spectrophotometric methods,[522] and formation constants have been determined. The neutral deprotonated complex (**167**) was characterized in the solid state.

The hydration of acetaldehyde is catalyzed by zinc(II) and the catalysis is enhanced by the presence of anions such as acetate and hydroxide.[523] Various processes were considered (Scheme 44) to account for the hydroxide-dependent and -independent pathways involving zinc(II). Zinc(II)

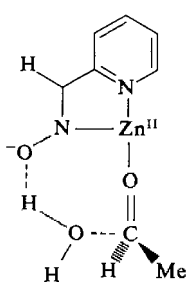


Scheme 44

catalysis of the hydration of acetaldehyde has been shown to be markedly increased by a ligand carrying a remote general base.[524] This result provides evidence that hydration when cooperatively catalyzed by zinc(II) and a base requires independent attack by base and metal ion, that is the base must not be coordinated to the metal ion. This system involved the use of the zinc complex of the pyridine-2-aldoximate ion ($pyox^-$ = **168**). Catalysis is believed to involve general base-



(**168**) = $pyox^-$

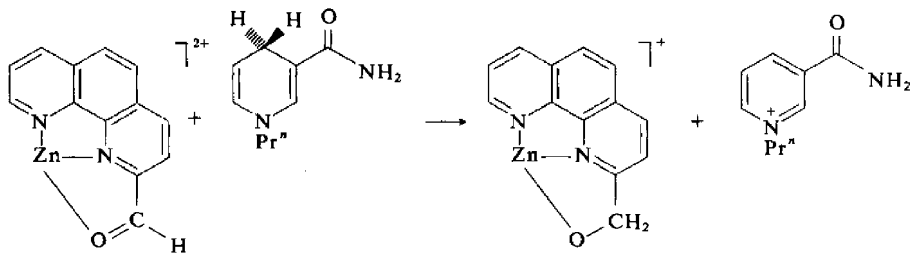


(**169**)

catalyzed attack at the carbonyl group which is already polarized and thus activated by the zinc ion (**169**). The remote general base increases the activity of zinc(II) by a factor of *ca.* 2×10^2.

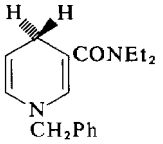
61.4.22 METAL ION-PROMOTED CARBONYL REDUCTIONS

The NAD^+-dependent alcohol dehydrogenase from horse liver contains one catalytically essential zinc ion at each of its two active sites. An essential feature of the enzymic catalysis appears to involve direct coordination of the enzyme-bound zinc by the carbonyl and hydroxyl groups of the aldehyde and alcohol substrates. Polarization of the carbonyl group by the metal ion should assist nucleophilic attack by hydride ion. A number of studies have confirmed this view. Zinc(II) catalyzes the reduction of 1,10-phenanthroline-2-carbaldehyde by *N*-propyl-1,4-dihydronicotinamide in acetonitrile,[526] and provides an interesting model reaction for alcohol dehydrogenase (Scheme 45). The model reaction proceeds by direct hydrogen transfer and is absolutely dependent on the presence of zinc(II). The zinc(II) ion also catalyzes the reduction of 2- and 4-pyridinecarbaldehyde by $Et_4\overset{+}{N}\ BH_4^-$.[526] The zinc complex of the 2-aldehyde is reduced at least 7×10^5 times faster than the free aldehyde, whereas the zinc complex of the 4-aldehyde is reduced only 10^2 times faster than the free aldehyde. A direct interaction of zinc(II) with the carbonyl function is clearly required for marked catalytic effects to be observed.



Scheme 45

The reduction of (*E*)-2-, (*E*)-3- and (*E*)-4-cinnamoylpyridines by 1,4-dihydropyridines to give dihydro ketones has also been shown to be catalyzed by zinc(II) and magnesium(II).[527] Kinetic measurements show that the rate of reduction is fastest in the case of the 2-isomer where the metal is simultaneously complexed with the nitrogen and oxygen donors. A very fast zinc-catalyzed reduction of pyridine-2-carbaldehyde by the alcohol dehydrogenase coenzyme model *N,N'*-diethyl-*N*-benzyl-1,4-dihydronicotinamide (**170**) has also been described.[528]

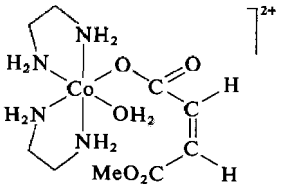


(**170**)

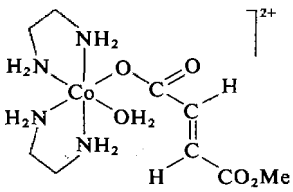
61.4.23 METAL ION-PROMOTED REACTIONS OF ALKENES

Nucleophilic attack at an alkene is not a favoured process in organic chemistry. Forcing conditions are required, such as high concentrations of a strong base and/or high temperatures.[529] Biological reactions are, however, known where alkenes are rapidly hydrated or aminated in near neutral conditions and ambient temperatures. Some of these enzymic systems involve metal ions and as a result there has been an interest in developing suitable model systems using metal complexes.

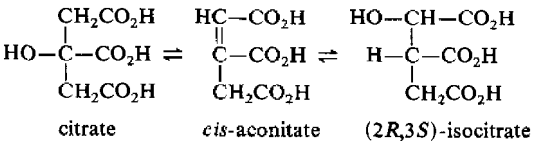
The enzyme aconitase catalyzes the isomerization of citric acid to isocitric acid *via* the intermediate *cis*-aconitic acid (Scheme 46),[530] and various attempts have been made to model this reaction.[21] The cobalt(III) complexes derived from methyl maleate (**171**) and methyl fumarate (**172**) have been prepared[531] to study intramolecular attack by coordinated hydroxide on the alkene. Generation of the hydroxo species of the maleic acid complex leads to rapid cyclization to give the



(171)



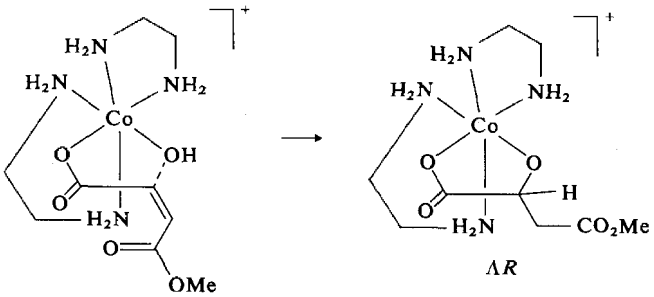
(172)



citrate *cis*-aconitate (2*R*,3*S*)-isocitrate

Scheme 46

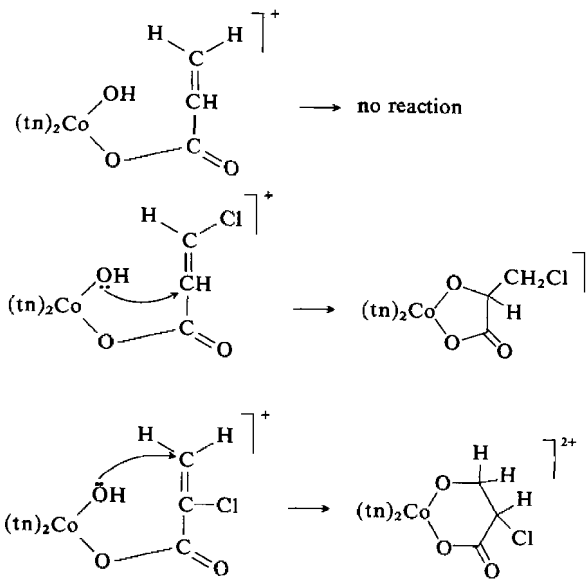
chelated malate half ester in two diastereoisomeric forms (ΛS and ΛR). The crystal structure of the ΛR isomer has been determined,[532] and the reactions leading to its formation are shown in Scheme 47. In 0.2 M imidazole buffer at pH 8 the rate constant for cyclization is *ca.* 0.1 s^{-1} at 25 °C, some 10^7-fold greater than that for hydration of the uncoordinated half ester under the same conditions. The cyclization gives exclusively the five-membered chelate, and the rate is independent of pH in the range 8–11 as would be predicted for such an intramolecular reaction. Tracer studies have also shown that bound $^{18}OH^-$ is retained in the chelated malate.



ΛR

Scheme 47

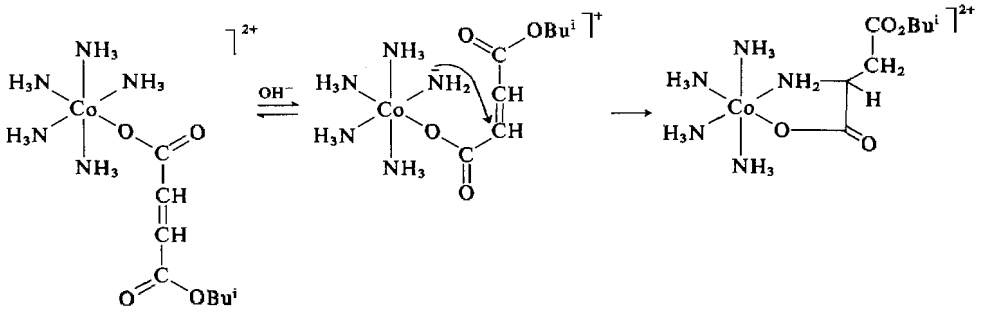
Superficially, it might be expected that coordinated acrylic acid would undergo a similar type of hydration reaction with nucleophilic addition taking place at the β-carbon (the acid is ester-like when coordinated). Experimentally[21] hydration is not observed (Scheme 48), but both the 2- and



Scheme 48

3-chloroacrylato complexes are hydrated by this intramolecular process. The latter gives a five-membered chelate ring while the former gives a six-membered ring. Interestingly the five-membered ring appears to be formed more slowly than the six-membered ring.

A consequence of the addition of coordinated OH^- to alkenes is that other nucleophiles, for example a coordinated aminate ion, should also be active. This type of reaction is seen with the chloropentaammine complex $[Co(NH_3)_5OOCCH{=}CHCO_2Bu^i]^{2+}$ in aqueous base[533] (Scheme 49). The reaction of the *t*-butyl maleate complex occurs to the extent of *ca.* 50% and is complicated by hydrolysis of the maleate ester and some decomposition of the cobalt(III) complexes. Reactions of this type have recently been exploited in the synthesis of β-carboxyaspartic acid in the coordination sphere of cobalt(III).[534]

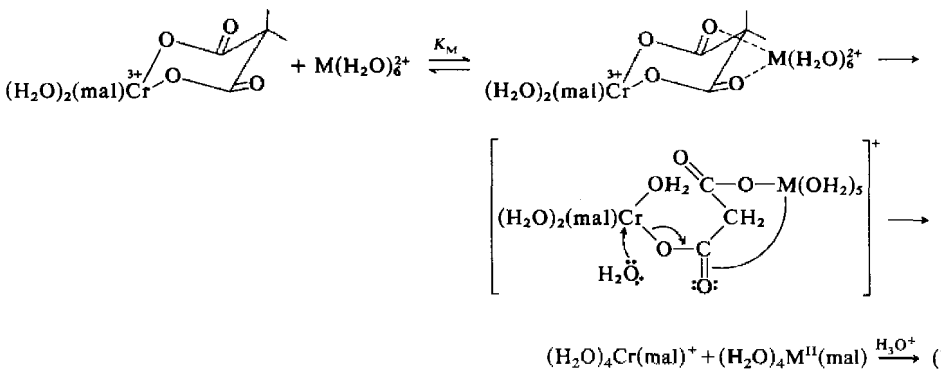


Scheme 49

61.4.24 ISOMERIZATION AND CHELATE RING OPENING

The acid-catalyzed aquation of *cis*-$[Cr(mal)_2(OH_2)_2]^-$ to give $[Cr(mal)(OH_2)_4]^+$ has been studied in detail.[535] The Cu^{II}-, Ni^{II}-, Co^{II}- and Zn^{II}-catalyzed dissociation of the *cis*-diaquabis(malonato)chromate(III) ion has also been recently investigated using perchloric acid solutions.[536] Under these conditions $k_{obs} = k_H[H^+] + k_M[M^{2+}]$ where k_{obs} is the observed first order rate constant and k_H and k_M are the appropriate rate constants for the proton- and metal ion-catalyzed pathways respectively. The metal ions exert marked catalytic effects with k_M values following the sequence $Cu^{II} > Ni^{II} > Co^{II} > Zn^{II}$. Saturation kinetics were not observed. A possible mechanism for the reaction is outlined in Scheme 50. Metal ion-catalyzed aquation of tris(malonato)chromate(III) has also been investigated.[537] In perchloric acid solutions ($[H^+] = 0.05$ M), $k_{obs} = k_H[H^+] + k_M[M^{2+}]$, with values of k_M following the sequence $Cu^{II} > Ni^{II} > Co^{II} > Zn^{II} > Mn^{II}$. The k_M values parallel the formation constants for the mono complexes of the metal ions with malonate. A similar mechanism to that shown in Scheme 50 is predicted for this reaction. A number of other studies on metal ion-catalyzed aquation of Cr^{III} complexes have also been published.[538,539]

The *trans* ⇌ *cis* isomerization of $[Cr(C_2O_4)(H_2O)_2]^-$ is also catalyzed by metal ions and a detailed study of catalysis by Mg^{II} has been published.[540] Dissociation of oxalato complexes of Cr^{III} of the type $[Cr(ox)_n(OH_2)_{6-2n}]^{(3-2n)+}$ $(n = 1, 3)$ is also promoted by a series of transition metal ions.[541]



$$(H_2O)_4Cr(mal)^+ + (H_2O)_4M^{II}(mal) \xrightarrow{H_3O^+} (H_2O)_6M^{2+} + H_2mal$$

Scheme 50 Possible mechanism for the metal ion-catalyzed aquation of *cis*-$[Cr(mal)_2(H_2O)_2]^-$

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61.5

Decomposition of Water into its Elements

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61.5.1 INTRODUCTION

61.5.1.1 General Considerations

Ever since Nehemiah demonstrated, albeit with divine assistance, that naphtha would burn,[1] man has increasingly relied on oil and oil based products for fuel as well as for feedstocks for the chemical industry. However, it was not until the invention of the internal combustion engine in the latter part of the 19th century that total exploitation of this resource became a reality.

Oil can therefore best be seen as the raw material of the 20th century and its exploitation increased almost exponentially until 1973 when the price was suddenly raised and people began to consider the likely future availability of this commodity. Predictions based on consumption at that time suggested that available or exploitable resources were probably only sufficient for a maximum of 50 years.

Ten years have passed since then and substantial economies in the use of oil have been made but it is still clear that oil has a limited lifetime as our major source of energy. Indeed the most pessimistic current forecasts suggest that alternatives will have to make the major contribution in about 60 years.

The major alternative is coal but this is also a non-renewable energy source with a predicted useful lifetime of about 200 years.

Whatever the timescale, both of these resources are non-renewable and the realization that their lifetime may be comparatively short, together with the economics of exploiting, for example, shale oil and sincere worries about the use of nuclear power have led scientists to search for renewable sources of energy which might be exploitable on a commercial basis.

Most renewable energy options must rely on a net input of energy into the earth and since the sun is our only external energy source, harnessing its energy is the main objective of almost all alternative energy strategies. Exceptions are tidal power, which relies on the gravitational attraction of the sun and particularly the moon, and geothermal energy, which cannot really be described as renewable.

The sun can be considered to emit radiation as a black body at about 5900 °C hence the solar emission spectrum has a maximum at 500 nm and extends into the IR and the UV regions of the electromagnetic spectrum, although most of the energy is in the form of visible light. Absorption processes in the atmosphere, mainly by H_2O and CO_2, remove a large proportion of the IR region of the sun's energy before it reaches the surface of the earth so that the main energy available at sea level is in the visible region (see Figure 1).

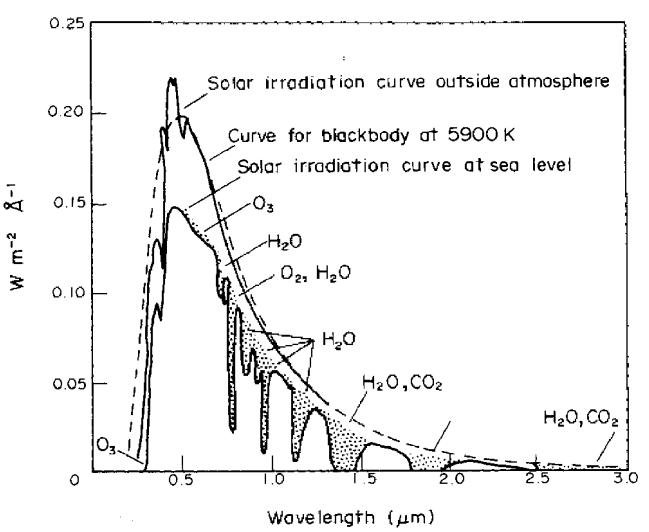


Figure 1. Spectral distribution curves related to the sun. Shaded areas indicate absorption at sea level due to the atmospheric constituents shown (reproduced from ref. 2)

The main drawbacks to the use of solar energy are its rather low density (*ca.* 1 kW m^{-2} on a clear day with the sun directly overhead), its wide wavelength spread and its somewhat unpredictable nature caused by different weather patterns. Nevertheless, calculations have shown that it is in theory possible to provide the energy needs of the whole world provided that the energy can

be stored in a usable form and that this storage process has an efficiency of ~10%. Under these circumstances, it would be necessary to cover 1% of the land area of the earth with solar collectors or an area of about the size of Quebec province in Canada.[2]

Despite this apparently optimistic assessment, it is probably more realistic to think in terms of solar energy making a contribution, along with many other processes, to our major energy needs. In particular, isolated communities in areas where sunshine is prevalent may depend on solar energy in the near future (indeed satellites already do), whilst more general exploitations will increase once the prices of coal and oil start to rise again.

There are very many options available for solar energy storage but this chapter is concerned solely with the use of solar energy to decompose water into hydrogen and oxygen, the former of which will be used as a fuel (see equation 1).

$$H_2O \rightarrow H_2 + 0.5O_2 \qquad \Delta G^\circ = 238\ \text{kJ mol}^{-1} \tag{1}$$

Solar hydrogen production from water has a number of extremely attractive properties. These include the fact that water is highly abundant and hence cheap and is regenerated on burning hydrogen so that no raw material is consumed. Hydrogen has a very high fuel value — the reverse of equation (1) produces 287 kJ of heat for every 2 g of hydrogen burnt. Hydrogen is easily stored, transported and used. Indeed feasibility studies suggest that the natural gas pipelines currently in use in the United States could be converted for transport of hydrogen gas with little or no modification.[2] Hydrogen could be burnt in stoves and a number of manufacturers have demonstrated the feasibility of hydrogen powered aircraft and motor cars.[3] It is considered that underground storage in large caves is also practical for hydrogen.[2]

When burnt, hydrogen is essentially non-polluting: the oxides of nitrogen that can be produced when hydrogen burns in air can be reduced to a minimum by efficient carburetion. Finally, hydrogen is indefinitely kinetically stable at room temperature so that long term storage is straightforward.

The main disadvantage to storage of solar energy in the form of hydrogen is that consumers believe that hydrogen is a highly dangerous commodity. Most people's only knowledge of hydrogen is associated with explosions, *e.g.* of the R101 airship. The actual dangers are vastly overstated since massive explosions only occur if hydrogen is mixed with oxygen in a 2:1 ratio. Even then, the very low density of hydrogen means that the explosion tends to go upwards and causes little damage on the ground. In contrast, fires and explosions arising from petroleum fumes are much more dangerous since they tend to cling to the ground and incinerate everything in the vicinity.

Hydrogen derived from water can, thus, be considered as a viable fuel or method for storing solar energy, provided that it can be produced cheaply. Some excellent books are available on the background to a hydrogen based fuel economy.[2-6]

61.5.1.2 The Thermodynamics of Hydrogen Production from Water

Hydrogen can easily be produced from water since all electropositive metals give hydrogen on treatment with water or dilute acid. Indeed, in 1785, during the course of experiments on large scale hydrogen production, Lavoisier used the observation that hydrogen was produced when water was contacted with hot iron as a crucial piece of evidence that water was a compound and not an element as had previously been supposed.[7] These and other experiments led to the development of many of the current theories of chemistry and to the overturning of the phlogiston theory.

However, reactions between metals and water lead to metal oxides as the other product and release of oxygen from these is very difficult, particularly since the thermodynamics are unfavourable.

For large scale commercial hydrogen production from water it is thus essential that the water is decomposed to produce hydrogen *and oxygen* (equation 1). The thermodynamics of this reaction are highly unfavourable, as is essential if hydrogen is to be a useful fuel, and it can be shown that temperatures in excess of 2800 °C are required for the direct thermolysis. However, it is possible to design cyclic thermal systems involving simple chemical transformations that operate at much lower temperatures (700–1000 °C) and research into the use of solar heat for these reactions is advancing. These reactions will not be considered further since, in general, they do not involve coordination compounds on account of the low stability of these compounds at high temperatures.

Alternative methods for surmounting thermodynamic barriers such as that of equation (1) are electrolysis and photolysis. Electrolysis is particularly attractive since hydrogen and oxygen are produced in different places and hence no separation process is required. However, electricity input is necessary and this must be generated. For solar energy conversion, direct photovoltaic conversion of sunlight into electricity using, for example, silicon cells is possible and subsequent electrolysis of water has been demonstrated. Alternatively, photoelectrochemical cells can be used and some of these are discussed later in this chapter, as are catalysts which lower the overpotential for hydrogen production at a mercury electrode.

Finally, direct photolysis of water is a possible and highly attractive means of storing solar energy, particularly since the major portion of the solar energy arriving on earth is of an energy comparable to electronic energy level differences within molecules.

On account of the quantized nature of light, any photochemical reaction will have a threshold wavelength (λ_g) such that light of longer wavelength will not drive the reaction.[8] If we assume that all light with wavelengths shorter than this threshold wavelength is absorbed and converted into chemical potential, it would appear at first sight that the amount of energy stored or the light energy to chemical energy conversion efficiency should increase as the threshold wavelength increases and, provided all the solar radiation were absorbed, 100% conversion efficiencies would be theoretically possible. However, this naive approach ignores the fact that quanta of light which have shorter wavelengths than the threshold wavelength contain more energy (hc/λ) than is necessary to drive the required reaction (hc/λ_g) and hence for each quantum an energy of $hc[(1/\lambda)-(1/\lambda_g)]$ is not used to drive the chemical reactions and must be dissipated as heat. The amount of this loss increases as the threshold wavelength increases (Figure 2) and the consequence of this is that a plot of conversion efficiency against threshold wavelength rises steeply to a maximum at *ca.* 840 nm and then falls slowly. Allowing for other unavoidable energy losses, the graph is as in Figure 3. The ripples on the high energy side of the maximum arise from absorption in the atmosphere. It should be noted that the absolute maximum conversion efficiency for solar radiation is *ca.* 31% and since this is a thermodynamic limit, efficiencies above this limit *cannot* be achieved.* In practice, losses caused during chemistry subsequent to the light absorption step will almost certainly cause a further reduction in the conversion efficiency. It is probably unrealistic to expect efficiencies in chemical storage systems to be higher than 20%.

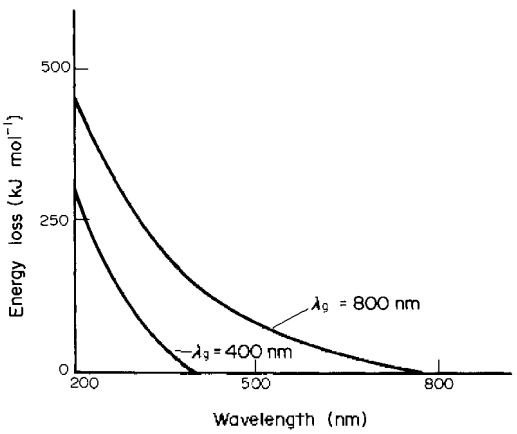


Figure 2 Plot of energy loss per mole of photons due to the quantized nature of light (E_{loss}) against wavelength for $\lambda_g = 800$ or 400 nm. Energy from all light of wavelength longer than the threshold wavelength is also lost

Turning to water photolysis specifically, it can easily be shown that, ignoring losses, the threshold wavelength for the breakdown of water into hydrogen and oxygen is 500, 1000 or 2000 nm depending upon whether one, two or four photons are used to decompose each molecule of water. These threshold limits are shown in Figure 3 by full vertical lines. Calculations which allow for unavoidable losses shift these values for two or four photons to 778 and 1352 nm (dotted lines in Figure 3) and further blue shifting will occur if the mechanism of decomposition involves, for example, energy wasting back reactions (discussed in detail below).[8] These threshold values are thermodynamic values and assume that hydrogen and oxygen are the primary products. If free

* If more than one reaction is used for photons of different energy, *e.g.* in stacked cells of different band gap semiconductors, higher efficiencies *can* be achieved but this is unlikely to be practical for direct *chemical* storage.

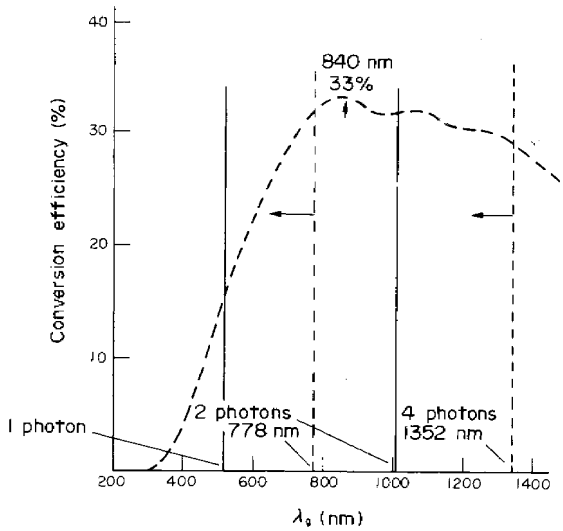


Figure 3. Plot showing the variation of solar energy conversion efficiency with threshold wavelengths at sea level. The solid vertical lines represent the energies required for decomposition of water using one or two photons per molecule of water respectively (4 photons would be at 2000 nm). The dashed vertical lines represent computed values for these threshold wavelengths taking into account unavoidable thermodynamic losses (adapted from ref. 8)

radical intermediates are involved, the threshold wavelengths are substantially shorter (<367 nm) and close examination of Figures 1 and 3 shows that systems in which free radicals are generated need not be considered for the practical storage of solar energy, where minimum efficiencies of *ca.* 12% will be required. Nevertheless, some systems of this kind are described in the subsequent sections of this chapter.

As discussed above, and considering Figure 3, it is clear that only systems which involve the use of two or four photons to decompose one water molecule need to be considered as practical candidates for efficient solar energy storage. However, the complexity of designing a four-photon system means that most attention has been given to the two-photon system.

One other important criterion for successful water cleavage that must be considered is the solution pH. Although the potential difference between the two half reactions for water decomposition is fixed at 1.23 V and is independent of pH, the half-cell reactions are dependent upon pH (Figure 4). Thus, by altering the pH of a solution it is sometimes possible to alter the half-cell potentials to be compatible with the redox properties of a photosensitizing catalyst. The oxidant must have a redox potential above the oxygen line, whilst the reductant must have a redox potential below the hydrogen line. The effect of pH is illustrated in subsequent sections of this chapter.

In the following sections of this chapter, we consider water decomposing systems based on simple inorganic ions or complexes, and then those which involve multistep intermolecular electron

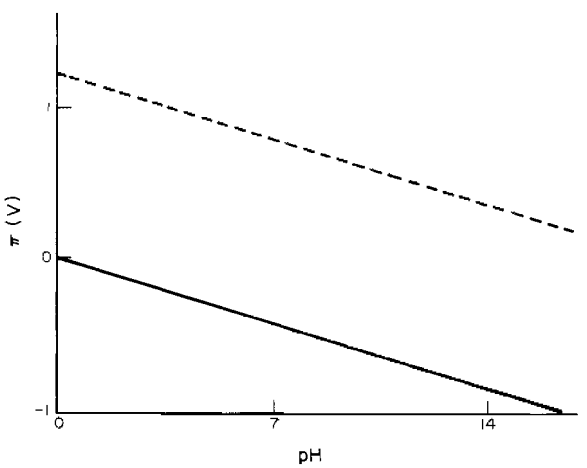


Figure 4. Variation of electrode potentials (π) with pH for hydrogen (——) and oxygen (- - -) production from water

Table 1 Hydrogen Production from Simple Metal Ions

Ion	*Reaction type*	*Wavelength (nm)*	*Conditions*	*Catalysts*	*Quantum yield*	*Other products*	*Refs.*
$Ti(OH)_3$	Δ	—	pH > 7	$Li^+ > Na^+ > K^+ > NH_4^+$ $Pt^{4+} \gg Ni^{2+} > Cu^{2+} > Co^{2+} > Fe^{2+}$ Ni > Pd, PtO_2	—	$Ti(OH)_4$	10, 11
Ti^{2+}	$h\nu$	—	—	—	—	—	12
Ti^{IV}	$h\nu$	<310	EtOH/H_2O	[Rh(en)$_2$Cl$_2$]Cl, [Rh(en)Cl$_3$]	—	Ti^{3+}	13
V^{2+}	Δ, $h\nu$	254	40–90% H_2SO_4 40–80% H_3PO_4	Ni > Pd, PtO_2	—	V^{3+}	12, 14–17
Cr^{2+}	Δ, $h\nu$	254	H_2SO_4	[Rh(en)$_2$Cl$_2$]Cl, [Rh(en)Cl$_3$] Ni > Pd, PtO_2 $[PdCl_4]^{2-}$, $[PtCl_4]^{2-}$	10^{-4}–0.15	—	12, 14, 17–20
Mn^{2+}	$h\nu$	254	pH < 1	—	—	—	17
Co^{2+}	$h\nu$	254	pH < 1	—	—	—	17, 21
Eu^{2+}	$h\nu$	366, 254	0.5 M HCl	Ni > Pd, PtO_2	0.02–0.3	Eu^{3+}	12, 22, 23
Eu^{2+}	Δ	—	—	Zeolite	—	—	24

transfers in attempts to model photosynthesis with synthetic reagents. We do not consider systems where the main components are naturally occurring nor do we consider unsensitized semiconductor systems.

61.5.2 WATER CLEAVAGE USING SIMPLE METAL SALTS AS CATALYSTS

61.5.2.1 Hydrogen Production

It is well known that a large number of metal ions, when placed in water, are capable of oxidizing or reducing water and that others can carry out the oxidation or reduction photochemically.

Simple ions capable of hydrogen production have been reviewed[9] and some of the results are listed in Table 1. In some cases, the reactions occur thermally but are accelerated by light, whilst in others the incident light provides the necessary thermodynamic driving force.

In general, the reactions proceed *via* metal to solvent (or metal to ligand, since the ligand and the solvent are the same) charge transfer, which leads to the production of H· or possibly solvated electrons, the latter of which subsequently react with H^+ to give H·. In many cases catalysts have been used to enhance the rate of the reaction, possibly by allowing it to proceed without the formation of free H· — either by forming adsorbed radicals (heterogeneous catalysts) or metal hydrides (homogeneous catalysts).

In all photochemical cases, UV light is required for hydrogen production and in most cases the reactions occur in strongly acidic solutions. Sulfuric, phosphoric, perchloric and nitric acids are the preferred media, although halo acids have occasionally been employed.

Usually, the metal containing products of these reactions are rather stable and do not produce oxygen thermally or photochemically, although isolated examples of hydrogen production on photolysis of higher oxidation state ions, *e.g.* Eu^{III},[25] U^{VI}[25] and Ti^{IV},[13] suggest that cyclic behaviour is occurring and this may also be the case for Mn^{II}.[26]

Nevertheless, the requirement for UV light and the generally stoichiometric nature of the reactions renders them unsuitable for solar energy storage. Cyclic systems based on $Fe^{II/III}$ and $Ce^{III/IV}$ are discussed in detail below.

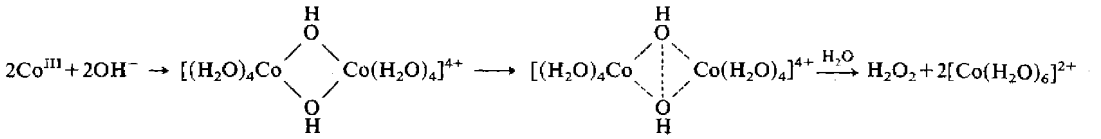
61.5.2.2 Oxygen Production

Table 2 lists a number of simple metal ions that have been used in the thermal or photochemical oxidation of water. Most of these contain metals in high oxidation states and are strong oxidizing agents. Recycling of these ions by thermal or photochemical means is, then, highly unlikely. The exceptions to this generalization are Co^{III} and Mn^{III}, the former of which, although strongly oxidizing in acid solution, is easily formed from Co^{II} in basic solution or if coordinated with high-field ligands. As yet catalytic cycles based on $Co^{II/III}$ have not been demonstrated but it is possible that some may be accessible. A cyclic water splitting reaction based on $Mn^{II/III}$ has reported.[26]

Table 2 Production of Oxygen from Water and Simple Metal Ions

Ion	*Reaction type*	*Conditions*	*Product*	*Refs.*
Tl^{3+}	$h\nu$	—	Tl^{+}	20
Mn^{IV}	Δ	H_2SO_4(6-15 M)	Mn^{III}	27
Co^{3+}	Δ	H_2SO_4(10^{-3}-3 M), $HClO_4$, HNO_3	Co^{2+}	28-31
Ni^{IV}	Δ	pH 1.0	Ni^{2+}	31
Cu^{3+}	Δ	pH 1.0	Cu^{2+}	31
Np^{VII}	Δ	$HClO_4$(0.1-4 M)	Np^{VI}	32
Pu^{VII}	Δ	pH > 7	Pu^{VI}	33, 34
Am^{IV}	Δ	H_3PO_4	Am^{III}	35
$[MnO_4]^-$	Δ	H_2SO_4(7.5 M)	Mn^{IV}, Mn^{III}	36
	$h\nu$	pH 7-14	MnO_2	37
$[FeO_4]^{2-}$	Δ	pH 0.5-8.8 $HClO_4$ or phosphate	Fe^{3+}	38

In general, the mechanism of O_2 production in these systems is believed to involve formation of OH· or oxygen formation by coupling of hydroxo bridges as shown in Scheme 1 for cobalt.[9]



Scheme 1 Proposed mechanism for the thermal oxidation of water by Co^{3+} [9]

61.5.2.3 Hydrogen and Oxygen Production

61.5.2.3.1 The Fe^{II}/Fe^{III} system

Redox potentials for various different Fe^{II}/Fe^{III} couples are shown in Table 3 and although $[Fe(OH)_2]$ is thermodynamically capable of reducing water to hydrogen and does so at elevated temperatures,[39] the rate of the reaction is low. It can, however, be increased by the addition of suitable catalysts, *e.g.* Ni salts,[39,40] excess $[FeSO_4]$,[40] metals such as Ni,[40] Cu,[40] Pd,[18,41] or colloidal Pt.[40] Nevertheless, cyclic water cleavage based on this system is unlikely since $[Fe(OH)_3]$ is a highly stable material.

Table 3 Half-wave Potentials (π^0) for Various $Fe^{3+/2+}$ Couples

Couple	π^0
$[Fe(H_2O)_6]^{3+/2+}$	+0.77
$Fe(OH)_3/Fe(OH)_2$	−0.88
$[Fe(CN)_6]^{3-/4-}$	+0.36
$[Fe(bipy)_3]^{3+/2+}$	+0.96

For catalytic water decomposition, it is therefore necessary to work in acidic solution where, although Fe^{II} is not thermodynamically capable of reducing water and Fe^{III} is not thermodynamically capable of oxidizing water, both reactions can be driven photochemically. Because of this, two photons are used for the reaction and a large portion of the solar spectrum can in theory be collected. In practice this is not the case as both Fe^{II} and Fe^{III} absorb mainly in the UV region of the spectrum.

Irradiation of aqueous solutions of Fe^{II} salts with UV light gives hydrogen and Fe^{III} with initial quantum yields in the range 0.1–0.7,* depending upon solution pH, although these decrease with time to 0.01 over prolonged periods.[42] It appears that it is essential for the iron to be present at least partly as $[Fe(SO_4)_n]^{2n-2}$ complexes since higher quantum yields are obtained at very low pH where these species predominate.[42,43] The quantum yield for H_2 production is generally rather insensitive to $[Fe^{II}]$ but at low pH (0.5) some positive dependence is observed.[42,43]

Studies carried out using deuterium labelling,[17] trapping reagents[44] or in glass matrices at low temperatures[9] confirm that hydrogen radicals are the primary product and are produced with quantum yields of *ca.* 0.1.[17] There is some suggestion that these react with Fe^{II} to form H^- from which hydrogen is obtained by protonation.[44]

The rate of hydrogen production is not increased by the addition of other simple ions but it can be sensitized to visible light by addition of $[Rh_2(bridge)_4]^{2+}$ (bridge = 1,3-diisocyanopropane). In this case, the hydrogen is produced directly from the rhodium species with formation of $[Rh_2(bridge)_4Cl_2]^{2+}$ and Fe^{II} simply regenerates this starting Rh catalyst.[45]

Oxygen production can also be achieved by irradiation of iron(III) salts with 254 nm light in aqueous solution. The greatest successes appear to occur using the perchlorate salt,[46] although the chloride has been employed.[47] It has been shown by detailed kinetic studies that the mechanism of this reaction involves primary formation of hydroxyl radicals, two of which give an oxygen atom. Dimerization of these atoms produces oxygen.[46] The success of the reaction probably arises because back electron transfer between OH· and Fe^{2+} is slow ($k < 3 \times 10^7$ dm^3 mol^{-1} s^{-1}).[46] The O_2 producing reaction can be catalyzed by WO_3, ZnO or TiO_2 but not by SiO_2 or Al_2O_3.[48] RuO_2 adsorbed on WO_3 seems to be an even more efficient catalyst[49] and it has been suggested that O_2 is not formed on photolysis of ammonium iron(III) sulfate unless these catalysts are present

* All quantum yields are quoted in mol einstein^{-1}.

Similar results were obtained with $[Fe(CN)_6]^{3-}$. The initial electron transfer event in these cases occurs between catalyst adsorbed Fe^{3+}(ads) and OH^-(ads).[48]

Combining these two half reactions leads to catalytic production of hydrogen and oxygen,[25,26] although quantum yields are very low (<0.001).[26]

61.5.2.3.2 The Ce^{III}/Ce^{IV} system

Although broadly similar results to those obtained with Fe^{II}/Fe^{III} have been obtained from Ce^{III}/Ce^{IV}, the thermodynamics of the system differ in one very important respect: both oxidation of OH^- by Fe^{III} and reduction of H^+ by Fe^{II} are thermodynamically uphill reactions, whereas oxidation of OH^- by Ce^{IV}, even in acid solution, is thermodynamically favourable although its rate is negligible in the absence of added catalyst or UV irradiation. At first sight this would appear to be to the advantage of the Ce^{IV} system but it means that only one photon is *required* for the cleavage of each water molecule (the other being employed to overcome a kinetic barrier) and hence only a fraction of the solar spectrum can, even theoretically, be converted.

Nevertheless, considerable effort has been expended on this system and the mechanism is as shown in equations (2)–(7),[25,50,51] although there is some question as to the exact nature of the O_2 producing species. Dimers,[52,53] ion pairs,[54] or adsorbed OH^- and Ce^{IV} ions[55] have all been proposed but coordination by sulfate is detrimental.[56] Using 254 nm irradiation, efficiencies as high as 36% have been observed for the thermodynamically favourable O_2 producing step[57] and O_2 has even been observed using solar irradiation.[58,59] The efficiency of the H_2 producing step is, however, very much lower ($\simeq$0.1%)[57] and H_2 is not observed using an array of parabolic mirrors for solar energy collection,[60] although apparently a black galvanized iron plate[61] used as collector does allow H_2 production from Ce^{III} as does direct focussed solar irradiation.[58] Catalysis of the thermal production of O_2 from Ce^{IV} is discussed in detail in Section 61.5.4.5 since this reaction has frequently been employed for evaluation of potential O_2 producing catalysts. Dye sensitization of the reaction of Ce^{III} with water does not appear to have been attempted.

$$Ce^{4+} + H_2O \rightleftharpoons [CeOH]^{3+} + H^+ \quad (2)$$

$$2[CeOH]^{3+} \rightarrow [Ce{-}O{-}Ce]^{6+} + H_2O \quad (3)$$

$$[Ce{-}O{-}Ce]^{6+} \xrightarrow{h\nu \text{ or } \Delta} Ce^{3+} + CeO^{3+} \quad (4)$$

$$[CeO]^{3+} + [Ce{-}O{-}Ce]^{6+} \rightarrow 3Ce^{3+} + O_2 \quad (5)$$

$$[Ce(H_2O)]^{3+} + H^+ \rightarrow [Ce(H_2O)\cdots H]^{4+} \quad (6)$$

$$[Ce(H_2O)\cdots H]^{4+} + [Ce(H_2O)]^{3+} \xrightarrow{h\nu} 2Ce(OH)^{3+} + H^+ + H_2 \quad (7)$$

61.5.3 WATER CLEAVAGE USING METAL COMPLEXES AS CATALYSTS

Complex metal ions which produce hydrogen on photolysis are listed in Tables 4 and 5. A large number of different metal ions has been investigated and selection of the correct ligands sometimes means that visible light can be used for H_2 production. Omitted from these tables are a large number of zinc dithiolene complexes which give hydrogen on photolysis in aqueous THF.[89] Apparently decomposition to ZnS occurs and much of the hydrogen is derived from the known[90] photoinduced dehydrogenation of THF in the presence of ZnS.[91]

In general, the complexes shown in Tables 4 and 5 are hydrides or generate hydrides within the reaction medium. Some of these require further discussion since they can take part in cyclic hydrogen production or the catalyst can easily be regenerated from the product of hydrogen production.

Of the mononuclear complexes perhaps the most interesting are $[IrCl_6]^{3-}$ and the complex cobalt hydrides since in both cases cyclic reactions have been observed. For $[IrCl_6]^{3-}$, hydrogen and chlorine are formed on irradiation with 254 nm light, apparently by processes involving free radicals (equations 8–15).[70] The photochemical excitation probably involves L–M charge transfer.

$$[IrCl_6]^{3-} + H^+ \rightleftharpoons [HIrCl_6]^{2-} \quad (8)$$

$$[HIrCl_6]^{2-} \xrightarrow{h\nu} [IrCl_6]^{2-} + H\cdot \quad (9)$$

$$H\cdot + [HIrCl_6]^{2-} \rightarrow H_2 + [IrCl_6]^{2-} \quad (10)$$

$$H\cdot + H\cdot \rightarrow H_2 \quad (11)$$

Table 4 Photochemical Hydrogen Production from Mononuclear Metal Complexes and Water

Complex	*Wavelength* (nm)	*Conditions*	*Quantum yield*	*Product*	*Refs.*
$[V^{II}(cysteine)]$	—	pH 7.5–8.5	—	$V^{III}(cysteine)$	62
$[Cr(trien)]^{2+}$	—	—	—	—	63
$[Fe(CN)_6]^{4-}$	—	pH 7, $[H_2PO_4]^-$/EtOH	0.1–1.0	$MeCHO + [Fe(CN)_6]^{4-}$	64
$[Co(C_2O_4)_3]^{3-}$	Δ	H_2SO_4 (10^{-1}–10^{-3} M), H_3PO_4, $HClO_4$	—	$[Co(C_2O_4)_2]^{2-}$	65
$CoCl_2/CN^-$	<550	pH 9.5–10.5	—	—	66
$[Co(CN)_5]^{3-}$	313	pH 7	—	$[Co(CN)_6]^{3-}$	67
$[CoH(CN)_5]^{3-}$	248	—	0.05	$[Co(CN)_5]^{3-}$	68
	274	—	0.3–0.5	—	71–73
$[CuCl_3]^{2-}$	254	H^+ (1 M)	—	$[CuCl_3]^-$	69
$[Ru(NH_3)_5(MeCN)]^{2+}$	254	pH 3.0	0.005	$[Ru(NH_3)_5(MeCN)]^{3+}$	70
$[IrCl_6]^{3-}$	356	HCl (12 M)	0.28	$[IrCl_6]^{2-}$	74–76
$[MH(PEt_3)_3]^+$, M = Pt or Pd	Visible	pH 1–12	—	$[M(H_2O)(PEt_3)_3]^{2+}$	74, 76
$[RhH_2(PPr^i_3)_2(H_2O)_2]^{2+}$		H_3PO_4 (pH 2.5)	—	$[RhH(PPr^i_3)_2(H_2O)_3]^{2+}$	

Table 5 Polynuclear Metal Complexes in Photochemical Hydrogen Production from Water

Complex	*Wavelength* (nm)	*Conditions*	*Quantum yield*	*Product*	*Refs.*
$[Mo_2Cl_8H]^{3-}$	254	HCl (3 M)	0.13	$[Mo_2(OH)_2(H_2O)_x]^{4+}$	77–80
	313		0.008		
$[Mo_2Br_8]^{4-}$	254	HBr (3 M)	0.043	$[Mo_2(OH)_2(H_2O)_x]^{4+}$	78, 79
			0.007		
$[Mo_2(SO_4)_4]^{4-}$	254	H_2SO_4 (2.5 M)	0.17	$[Mo_2(OH)_2(H_2O)_x]^{4+}$	78, 79, 81
$[Mo_2(H_2O)_n]^{4+}$	254	CF_3SO_3H (1 M)	0.035	$[Mo_2(OH)_2(H_2O)_x]^{4+}$	78, 81
$[Rh_2(bridge)_4]^{2+}$ [a,b]	546	HCl (12 M)	0.004	$[Rh_2(bridge)_4Cl_2]^{2+}$	45, 70, 79, 82–85
$[Rh_4(bridge)_8Cl_2]^{4+}$ [a]	546	HCl (12 M)	0.018	$[Rh_2(bridge)_4Cl_2]^{2+}$	45, 79, 80, 84–85
$[Rh_4(bridge)_8Br_2]^{4+}$ [a]	546	HBr (9 M)	0.022	$[Rh_2(bridge)_4Br_2]^{2+}$	79, 82, 84–85
$H_2[SiW_{12}O_{40}]$	Δ	H_2SO_4 (10^{-4}–6 M)	—	$H_4[SiW_{12}O_{40}]$	86
$[W_6O_{20}OH]^{5-}$ [c]	254	pH 7	0.017–0.05	W^V	87, 88

[a] bridge = 1, 3-diisocyanopropane.
[b] bridge = 1,3-diisocyano-pentane or hexane (ref. 82).
[c] Pt catalyst.

$$H\cdot + H^+ \rightarrow H_2^+ \quad (12)$$

$$H_2^+ + [IrCl_6]^{3-} \rightarrow H_2 + [IrCl_6]^{2-} \quad (13)$$

$$[IrCl_6]^{2-} + Cl^- \rightarrow [IrCl_6]^{3-} + Cl\cdot \quad (14)$$

$$2Cl\cdot \rightarrow Cl_2 \quad (15)$$

$[HCo(CN)_5]^{3-}$ gives hydrogen and $[Co(CN)_5]^{3-}$ on photolysis with 313 nm radiation but photolysis of the product with 254 nm radiation regenerates $[HCo(CN)_5]^{3-}$, probably with formation of cyanogen.[68]

Complex chlorocuprates, *e.g.* $[CuCl_2]^-$ and $[CuCl_3]^{2-}$, also give hydrogen on 274 nm photolysis in acid solution. A moderately stable hydride intermediate, perhaps $[HCuCl_2]^{2-}$, $[HCuCl_3]^{3-}$ or a polynuclear species, has been identified and this can also be formed by reaction of $[CuCl_3]^{2-}$ with $NaBH_4$.[71,72] Hydrogen is produced as this ion decomposes and it has been suggested that the reaction sequence is as shown in equations (16)-(20).[72] As with simple metal ions the major photochemical event is believed to be hydrated electron formation by a charge transfer to solvent reaction. Unfortunately, a cyclic system based on these reactions has not been demonstrated.

$$[CuCl_3]^{2-} \xrightarrow{h\nu} [CuCl_3]^- + e^- \quad (16)$$

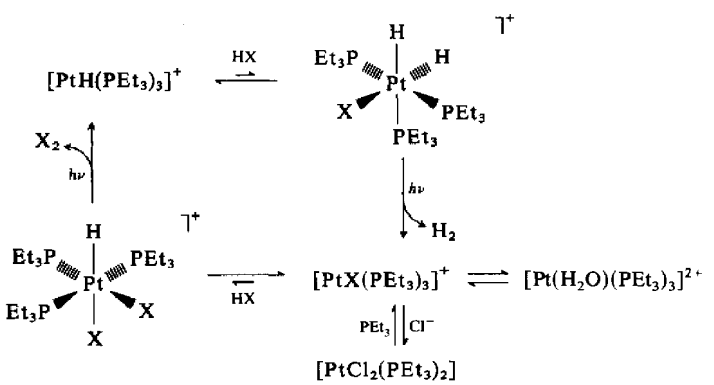
$$e^- + H^+ \rightarrow H\cdot \quad (17)$$

$$H\cdot + H\cdot \rightarrow H_2 \quad (18)$$

$$H\cdot + [CuCl_3]^{2-} \rightarrow [HCuCl_3]^{2-} \quad (19)$$

$$[HCuCl_3]^{2-} + H^+ \rightarrow H_2 + [CuCl_3]^- \quad (20)$$

Systems based on photolysis of $[MH(PR_3)_3]^{n+}$ (M = Pt or Pd, R = Et, $n = 1$; M = Rh, R = Pr^i, $n = 0$)[74-76] are also of interest since cyclic water cleavage has been reported for $[PtH(PEt_3)_3]^+$ in H_2SO_4.[75,76] Photolysis at 356 nm produces hydrogen and $[PtX(PEt_3)_3]^+$ (X = H_2O, $n = 2$; X = HSO_4 or Cl, $n = 1$) in a stoichiometric reaction,[14] whilst use of 254 nm light regenerates $[PtH(PEt_3)_3]^+$ and apparently produces $[S_2O_8]^{2-}$ or Cl_2. For $[S_2O_8]^{2-}$ oxygen can be generated by addition of Ag^+,[75,76] whilst Cl_2 apparently forms Et_3PO from excess PEt_3, which is required to prevent precipitation of $[PtCl_2(PEt_3)_2]$.[92] The mechanism of these reactions is shown in Scheme 2 and it is believed that the low rates of H_2 and X_2 production arise from the low equilibrium concentrations of the Pt^{IV} intermediates. Support for this comes from the observation that higher rates of hydrogen production are observed from the more nucleophilic $[RhH(PPr^i_3)_3]$, which is present in aqueous phosphoric acid in its protonated form $[RhH_2(PPr^i_3)_2(H_2O)_2)]^+$. Furthermore, photolysis can be carried out with visible light since the compound is yellow and the product of H_2 production is protonated rapidly to $[RhH(PPr^i_3)_2(H_2O)_3]^{2+}$.[74] Unfortunately, cyclic water cleavage has not been observed in this case. Nevertheless, systems of this kind offer scope for development since some fine tuning of both the photochemical and redox properties is possible by changing, for example, the nature of the substituents on the phosphine.



Scheme 2 Proposed mechanism for the photochemical decomposition of water catalyzed by $[PtH(PEt_3)_3]^+$; X = Cl^- or HSO_4^-[74-76]

For hydrogen production using visible light it appears that bi- or poly-nuclear complexes are more successful. Thus, $[Rh_2(bridge)_4]^{2+}$ (bridge = 1,3-diisocyanopropane) produces hydrogen with light of wavelength 546 nm.[47,70,79,82-85] The reaction is complex and some hydrogen is produced thermally in strong acid. The photochemical step is evidently production of H_2 and

$[Rh_2(bridge)_4Cl_2]^{2+}$ from $[Rh_4(bridge)_8Cl_2]^{4+}$, which is the product of the thermal hydrogen producing step. The starting $[Rh_2(bridge)_4]^{2+}$ can be regenerated[45,93] from $[Rh_2(bridge)_4Cl_2]^{2+}$ by reaction with Fe^{2+} and since Fe^{3+} can be used[94] for oxygen production catalyzed by, for example, $[ZnTMPyP]^{4+}$ (TMPyP = 5,10,15,20-tetra(*N*-methyl-4-pyridyl)porphyrin) and RuO_2/TiO_2, or by $[Ru(bipy)_3]^{2+}$ (bipy = 2,2′-bipyridyl) and RuO_2,[95] coupling of these reactions should lead to cyclic water cleavage. Unfortunately, however, the pH requirements of the two reactions (strong acid for H_2 production from $[Rh_2(bridge)_4]^{2+}$ and neutral or weak alkali for O_2 production from Fe^{3+}) mean that some development work would be required for successful sustained H_2 and O_2 production.

Dinuclear molybdenum complexes have also been employed for hydrogen production,[79] although cyclic reactions have not been observed in this case. In general UV irradiation gives higher quantum yields and hydrides, possibly formed by protonation of an excited state, are, once again, believed to be important. Interestingly, complexes with carboxylate bridging groups do not appear to be active,[77,80] although activity is obtained in the presence of monodentate or non-coordinating anions.

Cluster metal anions such as isopolytungstates, although *not* their molybdenum analogues,[87] have also been shown to be active for photochemical hydrogen production in the presence of platinum catalysts.[87] These complexes contain W^{VI} so that the photochemical event probably involves production of W^V and OH·,[87] identified by spin trapping techniques.[88] Hydrogen is then produced from W^V in a thermal reaction catalyzed by Pt. Reduced 12-silicon–tungsten heteropolyacids also produce hydrogen thermally from water in the absence of added catalyst.[86] These and related complexes catalyze the photochemical dehydrogenation of alcohols.[96] Curiously, these heteropolyacids do not produce hydrogen from water when adsorbed on an anion exchange resin, perhaps because of a distortion of the metal framework.[97]

Finally, catalytic hydrogen production from manganese porphyrin complexes using triphenylphosphine as an oxygen acceptor has been demonstrated.[98]

The number of complexes which produce oxygen from water is very small (see Table 6) and, since generally the products cannot be recycled, they are mainly of mechanistic interest. It is noteworthy that primary amines[99] and spermidine[100] do not inhibit O_2 production from Co^{3+} and that OH· can be produced even from the bridging oxygen atoms of the oxobipyridyl complexes.[101] Finally, saltm (*N,N′*-propylenebis(salicylideneaminato)) is the best of five Schiff bases for oxygen production from oxomanganese complexes and quinone — 45 others were inactive.[102]

Table 6 Oxygen Production from Metal Complexes

Complex	*Reaction type*	*Conditions*	*Product*	*Refs.*
$[Co(RNH_2)_5(H_2O)]^{3+}$	Δ	HNO_3	$[Co(RNH_2)_4(H_2O)_2]^{2+}$	99
$[Co(spermidine)(H_2O)_3]^{3+}$	Δ	1.0 M $HClO_4$	$[Co(spermidine)(H_2O)_3]^{2+}$	100
$[Mn_2O_2(bipy)_4]^{3+}$	313 nm	pH < 7	$[Mn_2O_2(bipy)_4]^{2+}$	101
$[Mn_2O_2(bipy)_4]^{4+}$	Δ	pH < 7	$[Mn_2O_2(bipy)_4]^{3+}$	101
$[Mn(saltm)(H_2O)]_2$	Visible	+quinone	$[Mn(saltm)_2O]$	102
$[Pt(H_2O)(PEt_3)_3]^{2+}$	254 nm	0.01 M H_2SO_4	$[PtH(PEt_3)_3]^+$	75, 76
$[\{(NH_3)_5RuO\}_2Ru(NH_3)_4]^{7+}$	Δ	pH > 7	'Ru red'	103

61.5.4 INTERMOLECULAR ELECTRON TRANSFER REACTIONS IN THE PHOTOCHEMICAL DECOMPOSITION OF WATER

61.5.4.1 General Considerations

Intramolecular electron transfer reactions for water decomposition, as described above, find little use for the storage of solar energy since, in general, UV light, very little of which is available from the sun at the earth's surface, is required.

More success in the photochemical decomposition of water using visible light has been achieved by attempting to mimic the photosynthetic processes by electron transfer, *via* a series of catalysts, from the excited state of a dye molecule to a proton. This is accompanied by oxidation of hydroxide ion by the oxidized form of the dye.

The potential for this kind of reaction was first recognized as early as 1921,[104] although the lack of suitable catalysts meant that these initial experiments were unsuccessful. Significant impetus was, however, given to this approach by two discoveries made during the mid 1970s.

Sutin and coworkers showed[105] that the excited state of $[Ru(bipy)_3]^{2+}$ was thermodynamically capable of reducing water whilst $[Ru(bipy)_3]^{3+}$ was also shown to oxidize water. They proposed the use of a photoelectrochemical cell to promote charge separation. Shortly afterwards, Whitten and coworkers demonstrated[106] that sustained hydrogen and oxygen production could be obtained on irradiation of monolayer assemblies of surfactant derivatives of $[Ru(bipy)_3]^{2+}$. Unfortunately, these results proved irreproducible[107-110] and it has been suggested that an impurity in some way assisted the reaction. This impurity has proved elusive, although various suggestions as to its nature have been made. These include $[RuH(CO)(bipy)_2]^{+}$[111] and $[RuCl(CO)(bipy)_2]^{+}$,[112] the latter of which is a photochemical water gas shift catalyst,[113] and an impurity in $[RuCl_2(bipy)_2]$ from which the surfactant monolayers had been synthesized.[106,114,115]

Despite the irreproducibility of Whitten's results, his and Sutin's observations have spawned enormous interest in $[Ru(bipy)_3]^{2+}$ as a sensitizer since it has λ_{max} at 452 nm — close to the emission maximum of the sun. Furthermore, its photochemically excited state has a long lifetime and is both strongly oxidizing and reducing. Finally, $[Ru(bipy)_3]^{3+}$, formed by oxidative quenching, is sufficiently oxidizing ($E^0 = 1.26$ V) to oxidize water.[116]

The majority of studies have led to the photochemical production of hydrogen or oxygen at the expense of a sacrificial electron donor or acceptor, but some systems for cyclic water cleavage have been reported.

More recently, water soluble zinc porphyrins which can absorb up to 45% of the solar radiation[117] have been studied[118] for both hydrogen and oxygen production.

61.5.4.2 Photochemical Hydrogen Production Mediated by $[Ru(bipy)_3]^{2+}$

61.5.4.2.1 Photochemical properties of $[Ru(bipy)_3]^{2+}$ and its excited states

Tris(2,2′-bipyridyl)ruthenium(II) dication ($[Ru(bipy)_3]^{2+}$) is one of the most extensively studied coordination compounds in chemistry due to its potential for use in cyclic photochemical water decomposition. An extensive review of the complex appears elsewhere.[116]

The properties which are of interest in this context are those connected with the generation and lifetime of the excited state, $[Ru(bipy)_3]^{2+*}$, and the redox potentials of this and the related Ru^{I} and Ru^{III} species.

The visible spectrum of $[Ru(bipy)_3]^{2+}$ shows an intense band at 452 nm which is assigned to a metal-to-ligand charge transfer (MLCT) absorption and which has an extinction coefficient of 1.4×10^4 dm^3 mol^{-1} cm^{-1}. Irradiation at this wavelength gives an excited singlet state species which rapidly intersystem crosses (with an efficiency of *ca.* 0.9) to give a relatively long-lived triplet state $[Ru(bipy)_3]^{2+*}$ ($\tau = 685$ ns).[116]

Measurements of the various redox couples (see Table 7) show that the excited state complex is *thermodynamically* capable of both oxidizing and reducing water at pH 7. Furthermore, it is found that $[Ru(bipy)_3]^{+}$ is a stronger reducing agent and $[Ru(bipy)_3]^{3+}$ is a stronger oxidizing agent than $[Ru(bipy)_3]^{2+*}$.

Table 7 Redox Potentials for Various Ru^{II}/Ru^{III} Couples

Redox couple	π^0(V)
$[Ru(bipy)_3]^{3+/2+}$	1.26
$[Ru(bipy)_3]^{2+*/+}$	0.84
$[Ru(bipy)_3]^{3+/2+*}$	−0.84
$[Ru(bipy)_3]^{2+/+}$	−1.26

In practice, however, photolysis of aqueous solutions of $[Ru(bipy)_3]^{2+}$ produces neither hydrogen nor oxygen in the absence of added catalyst, and despite initial claims[106] to the contrary, this is also true for irradiation of monolayers of analogous cationic complexes containing surfactant bipyridyl ligands.[107-109]

Whilst $[Ru(bipy)_3]^{2+*}$ itself is incapable of splitting water, its electron-transfer properties have been utilized for hydrogen production in a series of reactions involving cocatalysts (see equations 21 to 26). The first step involves electron transfer from the excited state complex to an electron relay (R), which in its reduced form is capable (in the presence of a suitable heterogeneous redox catalyst) of reducing protons to hydrogen. The $[Ru(bipy)_3]^{3+}$ which is formed is then capable of

oxidizing OH^- to O_2, but this reaction is only sufficiently rapid to compete with back electron transfer from R^- if another redox catalyst is employed. Alternatively, the $[Ru(bipy)_3]^{3+}$ may be reduced by some sacrificial electron donor (D), which in its oxidized form decomposes (equations 24 and 25). Such sacrificial systems for H_2 generation have allowed the study of the effect of different sensitizers, relays and redox catalysts in the system and it is these that are described below.

$$[Ru(bipy)_3]^{2+} \xrightarrow{h\nu} [Ru(bipy)_3]^{2+*} \quad (21)$$

$$[Ru(bipy)_3]^{2+*} + R \xrightarrow{k_q} [Ru(bipy)_3]^{3+} + R^- \quad (22)$$

$$[Ru(bipy)_3]^{3+} + R^- \xrightarrow{k_b} [Ru(bipy)_3]^{2+} + R \quad (23)$$

$$[Ru(bipy)_3]^{3+} + D \xrightarrow{k_{red}} [Ru(bipy)_3]^{2+} + D^+ \quad (24)$$

$$D^+ \rightarrow \text{decomposes} \quad (25)$$

$$R^- + H^+ \xrightarrow[\text{catalyst}]{\text{redox}} R + 0.5H_2 \quad (26)$$

61.5.4.2.2 Photochemical hydrogen production via oxidative quenching of $[Ru(bipy)_3]^{2+*}$ by methylviologen (1,1'-dimethyl-4,4'-bipyridinium dication)

It has been known for some time[116] that various organic molecules will quench $[Ru(bipy)_3]^{2+*}$, but of all the compounds examined, methyl viologen (MV^{2+}) has been the most extensively studied especially in systems for photochemical generation of hydrogen. This is no accident and this depth of study owes much to several important factors.

The first concerns the MV^{2+}/MV^+ redox potential which has a value of −0.46 V. This potential lies between that of $[Ru(bipy)_3]^{3+/2+*}$ at −0.84 V and H^+/H_2 at −0.41 V (pH 7). Thus $[Ru(bipy)_3]^{2+*}$ can reduce MV^{2+} to MV^+, which can in turn reduce H^+ to $0.5H_2$. Secondly, the reduced form of MV^{2+}, the radical cation MV^+, is stable over a wide pH range and will not decompose.

That MV^{2+} is doubly positively charged is also of consequence, for whilst this results in a net repulsion from positively charged sensitizers, it does mean that in the event of successful electron transfer, both products are positively charged and are thus repelled from each other, leading to net product formation.

Finally it is worthwhile noting that MV^{2+} (also known as paraquat) is an effective herbicide which operates by intercepting an electron from photoexcited chlorophyll in photosystem I, preventing the plant from utilizing solar energy. There then exists an obvious parallel between the behaviour of MV^{2+} as a herbicide and its behaviour as an electron-transfer reagent in model systems for photochemical water decomposition.

Thus, equations (21) to (26) have been proposed for the photochemical generation of hydrogen from water employing $[Ru(bipy)_3]^{2+}$ as sensitizer and MV^{2+} as electron relay (R). The individual reactions are now considered in detail.

The value of the quenching rate constant (k_q) has been a topic of some debate, with values ranging from 5×10^8 mol^{-1} dm^3 s^{-1} to 1×10^9 mol^{-1} dm^3 s^{-1}[120] being quoted. A detailed study by Gaines[121] of the effect of ionic strength (μ) on this constant resolved the debate and showed that k_q increases with increasing μ (primary kinetic salt effect) as would be expected for a reaction between two doubly positively charged species. Thus the values of k_q in water and acetate buffer (0.1 mol dm^{-3}, pH 4.7) are 5.4×10^8 mol^{-1} s^{-1} and 6.5×10^8 mol^{-1} dm^3 s^{-1} respectively. The rate constant can rise as high as 3.7×10^9 mol^{-1} dm^3 s^{-1} in $NaClO_4$ (0.20 mol dm^{-3}). These results have since been confirmed by other workers.[122,123] The rate constant (k_b) for the back electron transfer is 5×10^9 mol^{-1} dm^3 s^{-1} and this, along with the electrostatic repulsion between sensitizer and relay, contributes to a cage escape quantum yield for MV^{2+} (ϕ_{CE}) = 0.25[123] (*i.e.* net photochemical yield of MV^+).

It may then be expected that, with the higher values of k_q obtained in media of high μ, ϕ_{CE} should also increase. However, work by Kalyanasundaram[123] showed that this is not the case and it was found that ϕ_{CE} dropped from 0.25 in water to 0.16 in Na_2SO_4 (1 mol dm^{-3}).

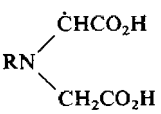
In order to prevent back electron transfer from MV^+ to $[Ru(bipy)_3]^{3+}$ and so maximize ϕ_{CE}, the Ru^{III} is reduced using a sacrificial electron donor such as triethanolamine (TEOA)[124] or ethylenediaminetetraacetic acid disodium salt (EDTA),[125] which when present in a high enough concentration can reduce Ru^{III} at a rate (k_{red}) which competes with k_b and leaves MV^+ formed as the stable product. The values of k_{red} for TEOA[124] and EDTA[126] are 4.7×10^7 mol^{-1} dm^3 s^{-1} and 1.1×10^8 mol^{-1} dm^3 s^{-1} respectively.

The yield of MV^{2+} also exhibits a pH dependence and is observed to fall at acid pH because of a reaction with $TEOA^+$ (equation 27), and because at acid pH, TEOA is protonated to $[TEOAH]^+$ which is a much poorer electron donor. Therefore, the rate of reduction of Ru^{II} would be expected to decrease with decreasing pH and this has indeed been found with k_{red} being 2.4×10^5 mol^{-1} dm^3 s^{-1}, 6.5×10^6 mol^{-1} dm^3 s^{-1} and 4.7×10^7 mol^{-1} dm^3 s^{-1} at pH 5, 7 and 9 respectively.[124] However, at alkaline pH, the yield of MV^+ may almost double[124] as a consequence of equations (28) and (29). A similar behaviour is observed for EDTA and in this case enhanced MV^+ production at high pH is thought[126] to occur by reaction of MV^{2+} with compound (**1**).

$$MV^+ + TEOA^+ \rightarrow MV^{2+} + TEOA \quad (27)$$

$$R_2\dot{N}CH_2CH_2OH(TEOA^+) \rightleftharpoons R_2NCH_2\dot{C}HOH + H^+ \quad (28)$$

$$R_2NCH_2\dot{C}HOH + MV^{2+} \rightarrow R_2NCH_2CHO + MV^+ + H^+ \quad (29)$$



(**1**)

Having maximized the yield of MV^+ one would expect to observe evolution of gaseous hydrogen according to equation (30).

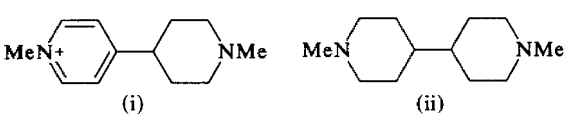
$$MV^+ + H^+ \rightarrow MV^{2+} + 0.5H_2 \quad (30)$$

In practice, however, although there is a small driving force for this reaction at pH 7, which increases with decreasing pH, a catalyst, usually colloidal Pt, PtO_2 or hydrogenase, is required to promote the oxidation of MV^+ by H^+ (see Section 61.5.4.4).

The operating pH for photolysis is governed by the reductant employed. For EDTA, the optimum pH is 5[126], whilst for TEOA it is 7.[124]

Thus, visible irradiation at pH 7 of 100 cm^3 of a solution containing $[Ru(bipy)_3]^{2+}$ (4.5×10^{-5} mol dm^{-3}), MV^{2+}(10^{-2} mol dm^{-3}), TEOA (0.05 mol dm^{-3}) and PtO_2 (2.3 mg) gave 0.40 cm^3 of hydrogen over 30 minutes.[124]

Prolonged photolysis of such systems would be expected to continue producing hydrogen until [reductant] fell to such a level that reaction (23) occurred faster than reaction (24). This is however not the case and the principle reason for cessation of hydrogen production is the hydrogenation of the aromatic rings of MV^{2+} to form piperidine derivatives catalyzed by Pt or PtO_2 (see Figure 5). Formation of such derivatives was inferred by several groups,[126–128] and they were finally identified using HPLC techniques.[129,130]



(i) (ii)

Figure 5. Compounds formed on hydrogenation of MV^{2+}

Studies by Hall and coworkers[131] had shown that in a system containing $[Ru(bipy)_3]^{2+}$, MV^{2+}, EDTA and colloidal Pt, the amount of hydrogen generated could be increased by the addition of small quantities of glutathione (γ-L-glutamyl-L-cysteinylglycine). As glutathione can itself act as an electron donor,[124,132,133] they interpreted their observations as a synergic effect of EDTA with glutathione. However, Sasse showed that the reason for this enhancement is quite different.[134]

It is known that divalent sulfur-containing compounds can affect the selectivity of hydrogenation reactions over Pt, if the S-donor/catalyst ratio is carefully controlled.[135] Thus, they found that addition of glutathione (5×10^{-5} mol dm^{-3}) to a solution of $[Ru(bipy)_3]^{2+}$ (5.5×10^{-5} mol dm^{-3}), MV^{2+} (1.6×10^{-3} mol dm^{-3}), EDTA (2×10^{-2} mol dm^{-3}) and colloidal Pt (5.1×10^{-5} mol dm^{-3}) decreased the percentage hydrogenation of MV^{2+} from 35 to 7% and increased its turnover from <100 to 420 (max 680 at [glutathione] = 5×10^{-4} mol dm^{-3}). A similar effect was observed on replacing glutathione with cysteine (5×10^{-5} mol dm^{-3}). The rate of hydrogen production was found to be essentially invariant with time and the electron donor properties of glutathione were shown to be insignificant by control experiments. Hence, it is the inhibition of MV^{2+} hydrogenation which accounts for the increased production of hydrogen. Hydrogenation of MV^{2+} can also be prevented by the use of a more specific catalyst such as RuO_2,[136] although it has proved to be less efficient for hydrogen production at pH 5 than platinum.

Some workers[126,137] have suggested the existence of the equilibrium represented by equation (31) in which both the forward and reverse steps are catalyzed by Pt. This was first demonstrated by passing H_2 through a solution of MV^{2+} in the presence of colloidal Pt, which led first to the formation of the deep blue MV^{+} and subsequently to hydrogenation to the piperidine derivative. This led to the postulation of MV^{+} as an intermediate in the hydrogenation of MV^{2+}.

$$MV^{+} + H^{-} \rightleftharpoons MV^{2+} + 0.5H_2 \tag{31}$$

Further studies on the equilibrium[137] revealed that reduction of MV^{2+} to its radical cation occurs quantitatively with excess hydrogen. Furthermore, irradiation of a hydrogen-saturated solution containing $[Ru(bipy)_3]^{2+}$ (5.5×10^{-5} mol dm^{-3}), MV^{2+}(10^{-3} mol dm^{-3}), EDTA (10^{-2} mol dm^{-3}) and Pt revealed a drop in the rate constant for hydrogen production of some four orders of magnitude with respect to a non hydrogen-saturated solution. These findings were confirmed by flash photolysis, which also showed that on removal of the hydrogen, the rate recovered to its original level. This inhibition by hydrogen (along with MV^{2+} hydrogenation) is reduced by photolyzing with a constant purge of an inert gas.

61.5.4.2.3 Photochemical hydrogen production via oxidative quenching of $[Ru(bipy)_3]^{2+}$ by chemically modified viologens*

The sacrificial hydrogen producing reactions described in equations (21) to (26) (above) have become accepted as constituting a 'model system' against which others are compared. One possible approach to the improvement of this system is to modify the properties of the electron relay chemically. Such modifications could result in a more negative redox potential of the radical anion facilitating hydrogen production at high pH, a change in water solubility of the reduced relay allowing the use of multiphase systems, more efficient quenching, better cage escape yields and resistance to hydrogenation.

In this section the effect of chemically modified viologens on the model system is described. Their role in the system is identical to that of MV^{2+} in the model system and hence the results of these modifications are collected in Table 8. Some of the findings are discussed below in more detail.

(i) Monomeric systems

By far the most impressive results from modified viologens were those of Grätzel and coworkers with tetradecylmethylviologen dication, $C_{14}MV^{2+}$ (compound **16**). Despite its long alkyl chain, the viologen shows little tendency to micellar aggregation,[138] but the reduced radical cation is much more hydrophobic and is solubilized by assemblies (see Section 61.5.4.7).

Thus, $C_{14}MV^{2+}$ quenches the excited state of $[Ru(bipy)_3]^{2+}$ with a rate constant $k_q = 8 \times 10^8$ mol^{-1} dm^3 s^{-1} and this is unaffected by cetyltrimethylammonium chloride (CTAC), up to concentrations of 5×10^{-2} mol dm^{-3}, indicating that mixed CTAC/$C_{14}MV^{2+}$ micelles are not formed.[139] In the absence of CTAC, k_b in this system is 4×10^9 mol^{-1} dm^3 s^{-1}, but flash photolysis showed that this drops to $k_b \leq 2 \times 10^7$ mol^{-1} dm^3 s^{-1} in micellar solution. Thus, the more hydrophobic radical cation, $C_{14}MV^{+}$, is solubilized by CTAC micelles, which, having a positive surface, do not allow approach of the oxidized $[Ru(bipy)_3]^{3+}$. This then gives an efficiency of 30% for the redox reaction. This study was extended by the removal of the CTAC from solution and the introduction of a Pt catalyst protected by a positively charged polysoap.[138] This work is described in Section 61.5.4.7.2.

In a comparative series of experiments, Amouyal *et al.*[142] studied the relationship between $E^0(R/R^{-})$ and k_q for compounds (**2**), (**3**) and (**4**) and others related to and including (**12**) and (**13**). They found that a correlation indeed existed, with k_q increasing as E^0 became less negative. However, this correlation did not extend to hydrogen production or turnover numbers of the viologen in a sacrificial hydrogen generation system.[120,143] In fact, these two quantities were found to be maximized when $-0.41\ V > E^0 > -0.50\ V$.

Working on viologens of related structures, Sasse and coworkers[144] confirmed these observations and went on to explain them in terms of k_q and the rate of hydrogen production *via* the reaction of the viologen radical cation with protons over the Pt catalyst. Thus, whilst k_q decreases with increasingly negative redox potentials of the viologen, the rate of hydrogen production increases, and it is the balance of these two rates which leads to the observed upper and lower limits of $E^0(R/R^{-})$.

Table 8 Electrochemical and Photochemical Properties of Various Viologen Type Electron Relays

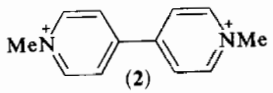
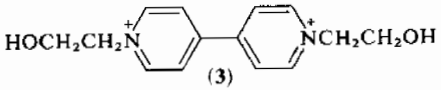
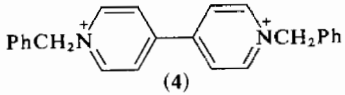
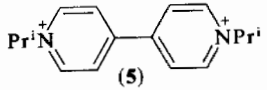
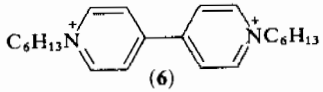
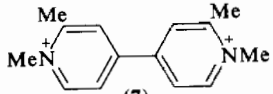
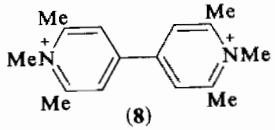
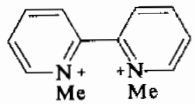
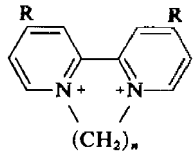
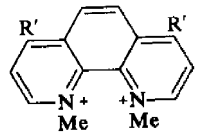
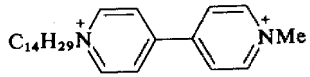
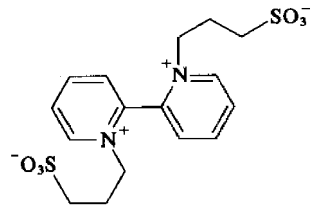
Compound	$\pi^0(R/R^-)$(V)	$k_q(10^8\ mol^{-1}\ dm^3\ s^{-1})$	$k_b(10^9\ mol^{-1}\ dm^3\ s^{-1})$	ϕ_{CE}	*pH*	*Refs.*
 (2)	−0.44	10.3	2.8	0.10[a]	5	120
 (3)	−0.40	10.9	1.19	—	5	120
 (4)	−0.36	14.6	2.32	0.14	5	120, 140
 (5)	−0.45	5.3	—	—	5	120
 (6)	−0.41	11.7	—	—	5	120
 (7)	−0.51	6.9	2.6	0.08	5	140
 (8)	−0.64	4.6	2.9	0.051	5	140
 (9)	−0.72	1.8	—	—	5	120

Table 8 Electrochemical and Photochemical Properties of Various Viologen Type Electron Relays (*continued*)

Compound	$\pi^0(R/R^-)$(V)	$k_q(10^8\ mol^{-1}\ dm^3\ s^{-1})$	$k_b(10^9\ mol^{-1}\ dm^3\ s^{-1})$	ϕ_{CE}	*pH*	*Refs.*
						
(10) R = H, $n = 2$	−0.55	5.74	2.81	—	5	120
(11) R = H, $n = 3$	−0.65	3.24	1.5	—	5	120
(12) R = Me, $n = 2$	−0.70	4.0	—	—	5	120
(13) R = Me, $n = 3$	−0.78	0.96	—	—	5	120
						
(14) R′ = H	−0.51	1.35	—	—	5	120
(15) R′ = Me	−0.40	10.8	—	—	5	120
 **(16)**	—	8.0	2.0 (0.02)[b]	0.3	—	139
 **(17)**	−0.75	5.9 (4.0)[c]	0.01[c]	0.024[c]	8.5	141

[a] Under the conditions employed.
[b] In the presence of CTAC micelle.
[c] In the presence of SiO_2 colloid.

Using the zwitterionic viologen (**17**) Willner and Degani[141,145] demonstrated the use of colloidal suspensions as an aid to charge separation. When a solution containing $[Ru(bipy)_3]^{2+}$, TEOA and (**17**; DQS) was irradiated at pH 9.6, no DQS^- formation was observed, but on the introduction of SiO_2 colloid into the system, DQS^- was produced with a quantum efficiency of 2.4%. Before excitation, the positively charged sensitizer is held in close proximity to the surface of the colloidal particle, which is negatively charged due to the ionization of the surface silanol groups at pH > 6. On electron transfer, DQS^- possesses a net negative charge and is therefore repelled by the colloidal surface. Not only does this facilitate charge separation, but it also results in a decrease in k_b to a value of about 10^7 mol^{-1} dm^3 s^{-1}. Addition of colloidal platinum to solutions containing $[Ru(bipy)_3]^{2+}$, TEOA, DQS and SiO_2 yielded hydrogen with a quantum efficiency of 2.2×10^{-3} at pH 8.5.

(ii) Polymeric systems

A logical extension of the work described above on long chain viologens, is to attach the viologen to a polymeric support and some examples of this are now described.

Work by Lee *et al.*[146] used *N*-(benzylpolyvinyl)-*N'*-methyl-4,4'-bipyridinium ($PVBV^{2+}$) with 41% of the benzyl groups having viologen functions, and polyvinyl-*N*-acetate-*N'*-methyl-4,4'-bipyridinium ($PVAV^{2+}$) with 40% of the acetate groups having viologen functions.

$PVBV^{2+}$ and $PVAV^{2+}$ quenched $[Ru(bipy)_3]^{2+*}$ with rate constants $k_q = 2.7 \times 10^8$ and 3.1×10^8 mol^{-1} dm^3 s^{-1} respectively, with $k_b = 1.8 \times 10^{10}$ mol^{-1} dm^3 s^{-1} in both cases. In the presence of EDTA, the yield of $PVBV^+$ on photolysis was 6.3% and in the presence of colloidal platinum (protected by the *in situ* polymer), the hydrogen yield was only 5% of that observed for an equivalent system containing MV^{2+} in place of $PVBV^{2+}$ and with the Pt supported by carbowax 20M. Matsuo and coworkers[147] examined poly(*N*-vinylbenzyl-*N'*-*n*-propyl-4,4'-bipyridinium) ($PV100^{2+}$) in conjunction with $[Ru(bipy)_3]^{2+}$ and the results are collected in Table 9. The quenching of $[Ru(bipy)_3]^{2+*}$ by $PV100^{2+}$ proceeded at a rate which was less than 20% of that for MV^{2+}, whilst the rate of hydrogen production in a sacrificial system was found to be 35% of that obtained for MV^{2+}. However, when k_q and the overall rate of hydrogen production are compared, it is found that $PV100^{2+}$ produces hydrogen twice as fast as MV^{2+} on reaction with H^+ over a Pt catalyst (equation 26). The same study also showed that the electron transferred to the viologen polymer is delocalized over the polymer chain, revealing the possibility of trapping the electron in an appropriate sink built into the polymer backbone.

Table 9 Comparison of Monomeric and Polymeric Viologens

Ru complex	*Viologen*	*Environment*	k_q(mol^{-1} dm^3 s^{-1})	*Relative rate of reduction*
$[Ru(bipy)_3]^{2+}$	MV^{2+}	Aqueous solution	1.7×10^9[a]	100[b]
$[Ru(bipy)_3]^{2+}$	$PV100^{2+}$	Aqueous solution	8.7×10^8	19

[a] Under the conditions employed. [b] Arbitrary units—reference.

In a slightly different system, Matsuo[148,149] also examined electron transfer to a polymer supported viologen [poly(*N*-vinylbenzyl-*N'*-*n*-butyl-4,4'-bipyridinium; PV^{2+}] *via* a zwitterionic viologen (*N,N'*-bis(3-sulfonatopropyl)-4,4'-bipyridinium; PSV).

PSV quenched 31% of the luminescence from $[Ru(bipy)_3]^{2+*}$ and gave a charge separation yield of 57% with respect to a control system using MV^{2+} as quencher. In the presence of PV^{2+}, however, whilst the quenching efficiency did not change (PV^{2+} does not quench $[Ru(bipy)_3]^{2+*}$ to an appreciable extent), the charge separation yield increased to 151% of that obtained in a system containing MV^{2+}. Similar effects were observed when $[Ru(phen)_3]^{2+*}$ was employed as sensitizer (phen = 1,10-phenanthroline). Furthermore, studies on the lifetime of the reduced form of PSV implied that the electron was further transferred to the polymer which was then acting as an electron sink.

In the presence of colloidal Pt, the decay of the reduced viologen was enhanced, presumably because of electron transfer to Pt and this decay became extremely rapid when the solution was acidified with 0.5 mol dm^{-3} H_2SO_4. However, when EDTA was added to the system, hydrogen production was not observed, as EDTA is not an efficient electron donor (to $[Ru(bipy)_3]^{3+}$) at this pH. Nevertheless, hydrogen was evolved on irradiation (in the presence of EDTA) at neutral pH, although much more slowly than in a system containing MV^{2+}, and in fact PV^+ accumulated. This points to proton reduction as the rate determining step and the effect is ascribed to a shift

in the redox potential of H^+/H_2 on Pt, which in this system is supported by PV^{2+}; similar shifts have been reported for Pt electrodes covered with ammonium salts.[150]

61.5.4.2.4 Hydrogen production via oxidative quenching of ruthenium(II) complexes containing chemically modified bipyridyl ligands

Much of the work in this area has centred around efforts to optimize the photochemical and redox properties of the Ru^{II} complexes which are related to water cleavage reactions, *e.g.* lifetime of excited state, absorption maxima, etc. A detailed account of these properties is found in Chapter 8.3 and hence it is only intended here to present the results of these studies on hydrogen producing systems.

Using $[Ru(bipy)_2(DECbipy)]^{2+}$ (DECbipy = diethyl-2,2′-bipyridine-4,4′-dicarboxylate), Sasse and coworkers[151] found that hydrogen production yields in a system comprising $[Ru(bipy)_2(DECbipy)]^{2+}/MV^{2+}$/EDTA/Pt were only 10% of those obtained in an identical system employig $[Ru(bipy)_3]^{2+}$. This decrease was attributed to two effects. Firstly, $E^0(Ru^{3+/2+*})$ for the DECbipy substituted complex was some 100 mV less negative than that of the unsubstituted complex, rendering the former a weaker reducing agent. This is reflected in the values of $k_q(MV^{2+})$ obtained, which were 9.6×10^8 and 1.3×10^8 mol^{-1} dm^3 s^{-1} for the unsubstituted and substituted complex respectively. This lower value of k_q, coupled with the observation that water would quench $[Ru(bipy)_3(DECbipy)]^{2+*}$, albeit with $k_q < 10^5$, is thought to be responsible for the low yields of hydrogen.

In a related study,[152] compounds of the formula $[Ru(bipy)_n(thpy)_{3-n}]^{2+}$ (thpy = 2-(thiazol-2′-yl-pyridine) were examined as chromophores. It was found that the rate of hydrogen production steadily decreased with increasing n, but the stability of MV^{2+} in the system was markedly enhanced. Usually, MV^{2+} in these systems is gradually consumed *via* catalytic hydrogenation over the Pt catalyst (see Section 61.5.4.2.2), although sulfur containing compounds have been shown to inhibit this reaction.[134,140] Thus, using $[Ru(bipy)_2(thpy)]^{2+}$ as chromophore, the rate of hydrogen production is 67% of that obtained for $[Ru(bipy)_3]^{2+}$, but the percentage of unhydrogenated MV^{2+} increases from 53 to 93.[152] Inhibition of the hydrogenation reaction is due to adsorption of some $[Ru(bipy)_2(thpy)]^{2+}$ onto the Pt catalyst, presumably *via* the sulfur atoms of the thpy ligand.

Various phenanthroline complexes of Ru^{II} have been examined as potential chromophores including 1,10-phenanthroline (phen), 5-chlorophen (5-Clphen) and 4,7-dimethylphen (dmphen).[153] All of these complexes have much longer lived excited states than $[Ru(bipy)_3]^{2+}$, notably $[Ru(dmphen)_3]^{2+}$ where the excited state is three times longer lived. In a system using hydrogenase as catalyst and a thiol as electron donor, the rate of production of MV^+ increased according to bipy < phen < 5-Clphen < dmphen. The rate of hydrogen production, however, followed a different series (phen < bipy ≈ 5-Clphen < dmphen) and the lack of correlation between $d[MV^+]/dt$ and $d[H_2]/dt$ is attributed[153] to the known inhibition of hydrogenase activity by phen complexes of ruthenium.[154]

Highly efficient quenching of (*N,N′*-didodecyl-2,2′-bipyridine-4,4′-dicarboxamide)-bis(bipyridyl)Ru^{II} ($[RuC_{12}B]$) has been reported using long chain or polymer bound viologens.[147] These systems are approximately twice as efficient as the $[Ru(bipy)_3]^{2+}/MV^{2+}$ combination, although hydrogen production has not been reported.

Using $[Ru(bipy)_3]^{2+}$ pendant on polystyrene, photoreduction of MV^{2+} was achieved[155] at *ca.* 25% of the rate attained in a $[Ru(bipy)_3]^{2+}/MV^{2+}$ system. Addition of HCl and Pt black to the former system led to hydrogen evolution, although efficiencies were not given.

Work by Lever and later Tazuke on bipyrazinyl and bipyrimidyl complexes of Ru^{II} is described in Section 61.5.4.2.6.

61.5.4.2.5 Hydrogen production via oxidative quenching of $[Ru(bipy)_3]^{2+*}$ by non-viologens

Whilst methylviologen and its derivatives have attracted much attention as electron relays in multicomponent hydrogen producing systems (see Sections 61.5.4.2.2 and 61.5.4.2.3), other compounds have been studied and it is these that are described here.

Lehn and coworkers[156,157] investigated the rhodium complex $[Rh(bipy)_3]^{3+}$, which on photolysis in solutions containing $[Ru(bipy)_3]^{2+}$, TEOA and K_2PtCl_4 produces hydrogen after a short induction period during which $[PtCl_4]^{2-}$ is reduced to Pt^0 (see below). They found that an

oxidative cycle (in Ru) operates with $[Rh(bipy)_3]^{3+}$ quenching $[Ru(bipy)_3]^{2+}$ with a rate constant $k_q = 3.5 \times 10^8$ mol^{-1} dm^3 s^{-1} ($E^0(Ru^{3+/2+*}) = -0.84$ V; $E^0(Rh^{3+/2+}) = -0.67$ V).

Reactions (32) to (38) were proposed for hydrogen production at pH 7 in the presence of excess bipy and involve the further reduction of $[Rh(bipy)_3]^{2+}$ to $[Rh(bipy)_2]^+$ and free bipy (reaction 36): TEOA· (produced after proton loss from $TEOA^+$ formed in reaction 34) was proposed as the source of the electron for the reduction to Rh^I. This Rh^I species is then protonated to a Rh^{III} hydride species (reaction 37), which reacts with H^+ to form hydrogen (reaction 38). Recoordination of a bipy ligand regenerates $[Rh(bipy)_3]^{3+}$ and completes the cycle. Reaction (38) can occur in the absence of platinum, although the rate of hydrogen production increases 20 fold in its presence.

$$[Ru(bipy)_3]^{2+} \xrightarrow{h\nu} [Ru(bipy)_3]^{2+*} \quad (32)$$

$$[Ru(bipy)_3]^{2+*} + [Rh(bipy)_3]^{3+} \xrightarrow{k_q} [Ru(bipy)_3]^{3+} + [Rh(bipy)_3]^{2+} \quad (33)$$

$$[Ru(bipy)_3]^{3+} + TEOA \rightarrow [Ru(bipy)_3]^{2+} + TEOA^+ \quad (34)$$

$$TEOA^+ \rightarrow \text{decomposes} \quad (35)$$

$$[Rh(bipy)_3]^{2+} + e^- \rightarrow [Rh(bipy)_2]^+ + bipy \quad (36)$$

$$[Rh(bipy)_2]^+ + H^+ \xrightarrow{H_2O} [RhH(H_2O)(bipy)_2]^{2+} \quad (37)$$

$$[RhH(H_2O)(bipy)_2]^{2+} + H^+ \xrightarrow[[Pt^0]]{bipy} [Rh(bipy)_3]^{3+} + H_2O + H_2 \quad (38)$$

At pH < 6, in the absence of excess bipy and with EDTA as electron donor, hydrogen production takes place by a different mechanism (reactions 32 to 37 and 39 to 42: for TEOA read EDTA). Presumably, the $[Ru(bipy)_3]^{3+}$ generated in reaction (40) is reduced by EDTA. However, the source of the electron in reaction (41) is unclear, although presumably it could arise from EDTA· formed by deprotonation of $EDTA^+$ in an analogous reaction to that described above for TEOA.

Further studies on the same system by Sutin and coworkers[158] implied some variation on the mechanisms proposed by Lehn.[157] Sutin found that whilst the quantum yield of $[Ru(bipy)_3]^{3+}$ formation with $[Rh(bipy)_3]^{3+}$ as quencher was 0.15, the quantum yield of $[Rh(bipy)_3]^{2+}$ was 0.3. This was interpreted in terms of reactions (43) to (46), where the TEOA· radical reduces the Rh^{III} species rather than the Rh^{II} species. Furthermore, the fact that the quantum yield of the final Rh^I photoproduct is 0.13 suggests that it is formed *via* disproportionation of $[Rh(bipy)_3]^{2+}$ and not by reduction of $[Rh(bipy)_3]^{2+}$ by TEOA.

$$[RhH(H_2O)(bipy)_2]^{2+} + H^+ \xrightarrow{H_2O} [Rh(bipy)_2(H_2O)_2]^{3+} + H_2 \quad (39)$$

$$[Rh(bipy)_2(H_2O)_2]^{3+} + [Ru(bipy)_3]^{2+*} \rightarrow [Rh(bipy)_2(H_2O)_2]^{2+} + [Ru(bipy)_3]^{3+} \quad (40)$$

$$[Rh(bipy)_2(H_2O)_2]^{2+} + e^- \rightarrow [Rh(bipy)_2]^+ + 2H_2O \quad (41)$$

$$[Rh(bipy)_2]^+ + H^+ \xrightarrow{H_2O} [RhH(H_2O)(bipy)_2]^{2+} \quad (42)$$

$$[Ru(bipy)_3]^{2+*} + [Rh(bipy)_3]^{3+} \rightarrow [Ru(bipy)_3]^{3+} + [Rh(bipy)_3]^{2+} \quad (43)$$

$$[Ru(bipy)_3]^{3+} + TEOA \rightarrow [Ru(bipy)_3]^{2+} + TEOA^+ \quad (44)$$

$$TEOA^+ \rightarrow TEOA\cdot + H^+ \quad (45)$$

$$[Rh(bipy)_3]^{3+} + TEOA\cdot \rightarrow [Rh(bipy)_3]^{2+} + \text{products} \quad (46)$$

With regard to the hydrogen producing reactions, it was proposed[158] that $[Rh(bipy)_3]^{2+}$ was the active species and this was supported by the following observations. Solutions of the bis(bipyridine)rhodium(I) species produced no detectable hydrogen when left in contact with Pt for extended periods. Secondly, under catalytic conditions with high [Pt], hydrogen is evolved and no Rh^I is observed, whilst at low [Pt], the yield of hydrogen drops and Rh^I is formed at its expense.

That the reduction of $[PtCl_4]^{2-}$ to Pt^0 is the cause of the observed[157] induction period in hydrogen production was shown by the following experiments. Replacement of K_2PtCl_4 by colloidal Pt^0 in a catalytic system resulted in hydrogen evolution with no induction period.[158] Secondly, the induction time for a catalytic solution containing K_2PtCl_4 (3×10^{-4} mol dm^{-3}) was equivalent to the time required to form 3×10^{-4} mol dm^{-3} of Rh^I (in the absence of K_2PtCl_4). Coupled with the observation that free bipy accumulates at early photolysis times, this latter observation points to $[Rh(bipy)_2]^+$ as the reductant.[158]

Other groups[159-161] have investigated various $[Co(cage)]^{3+}$ complexes as electron relays with varying degrees of success. Many of these species seem to quench by energy transfer or do not charge separate in the encounter complex[160] but a notable exception is $[Co(sepulchrate)]^{3+}$ ($[Co(sep)]^{3+}$).[159-161] This complex oxidatively quenches $[Ru(bipy)_3]^{2+*}$ with a rate $k_q = 3\text{–}6 \times 10^8$ mol^{-1} dm^3 s^{-1}, but the quantum yield for cage escape is 0.9 (*cf.* $\phi_{CE} = 0.25$ for MV^{2+})

and this is attributed[159] to the extra charge on the complex with respect to MV^{2+}. However, $[Co(sep)]^{3+}$ is not as good as MV^{2+} in hydrogen producing systems as it is orange in colour and acts as an inner filter. Furthermore, the thermodynamic driving force for proton reduction is only 25 mV compared to 160 mV for MV^{2+}.

Photolysis of buffered aqueous solutions of $[Ru(bipy)_3]^{2+}$ and $[Fe_4S_4(SCH_2Ph)_4]^{2-}$ (t^{2-}; a synthetic analogue of the iron–sulfur proteins found in photosystem I) generates hydrogen in the presence and absence of EDTA.[162] This latter result is particularly interesting as it implies that water itself is acting as both electron donor and acceptor, although the authors failed to observe simultaneous oxygen evolution, even on addition of unhydrated RuO_2. Furthermore, that the proposed mechanism (reactions 47 to 51) requires four photons to produce one mole of hydrogen necessarily limits the potential efficiency of the system.

$$2[Ru(bipy)_3]^{2+} \xrightarrow{h\nu} 2[Ru(bipy)_3]^{2+*} \quad (47)$$

$$[Ru(bipy)_3]^{2+*} + t^{2-} \rightarrow [Ru(bipy)_3]^{3+} + t^{3-} \quad (48)$$

$$[Ru(bipy)_3]^{3+} + OH^- \rightarrow [Ru(bipy)_3]^{2+} + 0.25O_2 + 0.5H_2O \quad (49)$$

$$[Ru(bipy)_3]^{2+*} + t^{3-} \rightarrow [Ru(bipy)_3]^{+} + t^{2-} \quad (50)$$

$$[Ru(bipy)_3]^{+} + H^+ \rightarrow [Ru(bipy)_3]^{2+} + 0.5H_2 \quad (51)$$

Ti^{3+} was reported to produce hydrogen *via* oxidative quenching of $[Ru(bipy)_3]^{2+*}$ with a quantum efficiency of *ca.* 0.1, with the Ru^{III} so produced oxidizing a second mole of Ti^{3+} to Ti^{IV} (as TiO^{2+}) in preference to oxidizing water.[163] However, the observation[163] that the solutions of $[Ru(bipy)_3]^{2+}$ used in the experiments produced hydrogen on photolysis (*i.e.* in the absence of Ti^{3+}) prompted other workers to reappraise the initial claims. They found[164] that the quantum efficiency (in the presence of Ti^{3+}) was $\leq 10^{-5}$ and whilst agreeing with the previously measured value of $k_q = 6 \times 10^6$ mol^{-1} dm^3 s^{-1}, interpreted the quenching mechanism as one of energy transfer. This was supported by the observation that the rate of reaction (52) was $\leq 10^6$ mol^{-1} dm^3 s^{-1}. Thus the rate constant for electron transfer to and hence reduction of Ti^{3+} by a better reducing agent than $[Ru(bipy)_3]^{2+*}$ is smaller than the observed k_q (Ti^{3+}) which is consistent with energy transfer. Furthermore, it was suggested[164] that the thermodynamically allowed reduction of water by Ti^{3+} in HCl (1 mol dm^{-3} reaction solution) was being catalyzed by the same impurities which were probably responsible for the observed[163] hydrogen production on photolysis of $[Ru(bipy)_3]^{2+}$ alone.

$$[Ru(bipy)_3]^{+} + Ti^{3+} \rightarrow [Ru(bipy)_3]^{2+} + Ti^{2+} \quad (52)$$

Recent studies by Cole-Hamilton and coworkers[165] have shown that a family of neutral heteropentalenes will quench $[Ru(bipy)_3]^{2+*}$ at rates which are typically an order of magnitude greater than those observed for MV^{2+}: this is attributed to a lack of electrostatic repulsion between the chromophore and the quencher. Further, the radical anion of a related compound (2,1,3-benzothiadiazole-4,7-dicarbonitrile), generated by direct photolysis in the presence of EDTA, has been successfully stabilized in CTAB micelles[166] revealing the possibility of very large charge separation yields for the sensitized reaction, especially when sensitized by a multi-negative chromophore.

61.5.4.2.6 Photochemical hydrogen production via reductive quenching of $[Ru(bipy)_3]^{2+*}$

One alternative approach to hydrogen photogeneration mediated by $[Ru(bipy)_3]^{2+}$ is to harness the strongly reducing nature of $[Ru(bipy)_3]^{+}$. This Ru^{I} species is more strongly reducing than $[Ru(bipy)_3]^{2+*}$ ($Ru^{3+/2+*} = -0.84$ V; $Ru^{2+/+} = -1.26$ V), is longer lived and presents the advantage that it can be incorporated into a totally homogeneous system.

Sutin and coworkers[167,168] showed that ascorbic acid (H_2A), Eu^{2+} and SO_3^{2-} all reductively quench $[Ru(bipy)_3]^{2+*}$ according to reactions (53) and (54).

$$[Ru(bipy)_3]^{2+} \xrightarrow{h\nu} [Ru(bipy)_3]^{2+*} \quad (53)$$

$$[Ru(bipy)_3]^{2+*} + Q \rightarrow [Ru(bipy)_3]^{+} + Q^+ \quad (54)$$

$$Q = H_2A,\ Eu^{2+} \text{ or } SO_3^{2-}$$

The quenching and back reaction rate constants as determined by flash photolysis, are collected in Table 10. Noteworthy here is the quenching by SO_3^{2-}, which proceeds by two parallel routes. The normal dynamic quenching (reaction 54) has a rate constant $k_q = 3 \times 10^5$ mol^{-1} dm^3 s^{-1} with

Table 10 Comparison of Various Electron Donors to $[Ru(bipy)_3]^{2+*}$

Q	$k_q(10^7\ mol^{-1}\ dm^3\ s^{-1})$	$k_b(10^7\ mol^{-1}\ dm^3\ s^{-1})$
Eu^{2+}	2.8	2.7
HA^-	2.0	100
SO_3^{2-} [a]	~0.03	<0.1

[a] Refers to dynamic process (see text).

$k_b \leq 10^6\ mol^{-1}\ dm^3\ s^{-1}$. However, some $[Ru(bipy)_3]^+$ is formed during the laser pulse and this is attributed to reactions (55) and (56).

$$[Ru(bipy)_3]^{2+*} + SO_3^{2-} \rightleftharpoons [Ru(bipy)_3]^{2+*}/SO_3^{2-} \quad (55)$$

$$[Ru(bipy)_3]^{2+*}/SO_3^{2-} \xrightarrow{h\nu} [Ru(bipy)_3]^{+} + SO_3^{-} \quad (56)$$

When the macrocyclic Co^{II} complex $[Co(Me_6[14]dieneN_4)]^{2+}(Co^{II}L)$ is added to such systems (where $Q = H_2A$ or Eu^{II}), then hydrogen is evolved on visible irradiation.[169] Thus on photolysis, a mixture of $[Ru(bipy)_3]^{2+}(1 \times 10^{-4}\ mol\ dm^{-3})$, Eu^{II} (0.1 mol dm^{-3}) and $Co^{II}L$ (4×10^{-3} mol dm^{-3}) in HCl (0.1 mol dm^{-3}) produces hydrogen with a quantum efficiency of 0.051. The proposed mechanism is given in reactions (57) to (60) and involves reduction of $Co^{II}L$ to $Co^{I}L$ by $[Ru(bipy)_3]^+$, regenerating $[Ru(bipy)_3]^{2+}$. The $Co^{I}L$ produced then forms a Co^{III} hydride which, in the presence of acid, liberates hydrogen leaving $Co^{III}L$ which is reduced to $Co^{II}L$ by a second mole of Eu^{2+}.

$$[Ru(bipy)_3]^{2+*} + Eu^{II} \rightarrow [Ru(bipy)_3]^{+} + Eu^{III} \quad (57)$$

$$[Ru(bipy)_3]^{+} + Co^{II}L \rightarrow [Ru(bipy)_3]^{2+} + Co^{I}L \quad (58)$$

$$Co^{I}L + H^+ \rightarrow [Co^{III}LH]^- \xrightarrow{H^+} Co^{III}L + H_2 \quad (59)$$

$$Co^{III}L + Eu(II) \rightarrow Co^{II}L + Eu(III) \quad (60)$$

$$\textit{Net:}\ \ 2Eu^{II} + 2H^+ \xrightarrow{h\nu} 2Eu^{III} + H_2 \quad (61)$$

However, the thermodynamics of reaction (61) in the absence of light are downhill by 0.43 V and hence the light is providing energy to overcome a kinetic barrier. If Eu^{II} is replaced by H_2A, then the quantum efficiency of hydrogen production drops by nearly two orders of magnitude. Nevertheless, the net reaction (reaction 65) is thermodynamically uphill by 0.41 V at $pH \leq 4$. The proposed reaction mechanism is now described by reactions (62), (63), (58), (59) and (64). The complexity of reduction reactions employing ascorbate are described elsewhere.[170]

$$[Ru(bipy)_3]^{2+*} + HA^- \rightarrow [Ru(bipy)_3]^{+} + HA\cdot \quad (62)$$

$$2HA\cdot \rightarrow HA^- + H^+ + A \quad (63)$$

$$Co^{III}L + HA^-\ (\text{or } H_2A) \rightarrow Co^{II}L + HA\cdot \quad (64)$$

$$\textit{Net:}\ \ H_2A \longrightarrow H_2 + A \quad (65)$$

The work was further extended to the replacement of $Co^{II}L$ by Co^{II} bipyridyls[171] (with H_2A as reductant) and in this case, quantum yields of up to 0.13 were recorded. Under the conditions used ($[Ru(bipy)_3]^{2+}/H_2A/Co^{2+}$/bipy), the principle Co species in solution are the mono- and bis-bipyridyl derivatives and the mechanism is analogous to that proposed for $Co^{II}L$, involving an unstable Co^{III} hydride species: some dihydrobipyridyl is also produced. Replacement of bipy by 4,4'-dimethyl-2,2'-bipyridyl (dmbp) increases the quantum yield, but substitution of Co^{2+} by Fe^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+} or Mn^{2+} leads to a substantial drop in hydrogen yields.

Fisher and Cole-Hamilton,[172] using a similar approach, employed $[PdH(PEt_3)_3]^+$ as the combined relay and catalyst (but not the Pt analogue), again using H_2A as the reductant. Aqueous solutions of $[PdH(PEt_3)_3]^+$ and its Pt analogue are known[74–76] to produce hydrogen on UV irradiation in reactions where M^{IV} dihydrides are the proposed intermediates (M = Pd or Pt), but in the multicomponent system a Pd^{I} hydride is invoked. The Pd^{I} species is generated according to reactions (66) to (68), whilst hydrogen production and Pd^{II} regeneration are as described by reactions (69) to (70), or reactions (71) to (73). The maximum quantum yield in this system is 1.8×10^{-3} at pH 4, although it is noted that hydrogen production ceases after 24 h due to substantial bleaching of the chromophore.

$$[Ru(bipy)_3]^{2+*} + HA^- \rightarrow [Ru(bipy)_3]^+ + A^{\cdot} + H^+ \quad (66)$$

$$H^{\cdot} + 2A^{\cdot} \rightarrow A + HA^- \quad (67)$$

$$[Ru(bipy)_3]^+ + [PdH(PEt_3)_3]^+ \rightarrow [Ru(bipy)_3]^{2+} + [PdH(PEt_3)_3]\cdot \quad (68)$$

$$[Ru(bipy)_3]^+ + [PdH(PEt_3)_3]\cdot + H^+ \rightarrow [Ru(bipy)_3]^{2+} + [Pd(PEt_3)_3] + H_2 \quad (69)$$

$$[Pd(PEt_3)_3] + H^+ \rightarrow [PdH(PEt_3)_3]^+ \quad (70)$$

$$2[PdH(PEt_3)_3]\cdot \rightarrow [(PEt_3)_3Pd(\mu\text{-}H)_2Pd(PEt_3)_3] \quad (71)$$

$$[(PEt_3)_3Pd(\mu\text{-}H)_2Pd(PEt_3)_3] \rightarrow 2[Pd(PEt_3)_3] + H_2 \quad (72)$$

$$2[Pd(PEt_3)_3] + 2H^+ \rightarrow 2[PdH(PEt_3)_3]^+ \quad (73)$$

Dithio anions[173] and tertiary amines have also been used reductively to quench $[Ru(bipy)_3]^{2+*}$ and Lehn and coworkers[174] reported a system using TEOA which was twice as efficient as the $[Ru(bipy)_3]^{2+*}/Co(dmbp)/H_2A$ system described above. Again, a cobalt complex, bis(dimethylglyoximato)cobalt(II) ($[Co(DMGH)]_2$) was employed as relay/catalyst and unstable Co^{III} hydride complexes were invoked as intermediates. Photolysis was carried out on solutions of Ru chromophore, TEOA (reductant), $[Co(DMGH)_2]$, and free $DMGH_2$ in DMF with a little acetic acid used to achieve a pH *ca.* 9. The origin of the hydrogen here is a little obscure. Curiously, addition of H_2O to such solutions (up to 20% by volume) decreased the yields of hydrogen by as much as 80%, suggesting that DMF may be the hydrogen source. Conversely, in MeCN the rate of hydrogen production increased when 20% H_2O was present, although it fell again with 50% H_2O. This system also suffers from instability due to consumption of $[Ru(bipy)_3]^{2+}$.

Interestingly, a similar system comprising solutions of $[Ru(bipy)_3]^{2+}$, $CoCl_2$ and CO_2 in $MeCN/H_2O/Et_3N$, simultaneously generates H_2 and CO on photolysis.[175] Hydrogen production was also achieved in a heterogeneous system,[176] employing tris(4,4'-dicarboxy-2,2'-bipyridyldiisopropylester)ruthenium(II) ($[RuL_3]^{2+}$) as sensitizer and Et_3N as the reductant. Thus, irradiation of sensitizer, reductant and PtO_2 in aqueous MeCN produced hydrogen with a quantum efficiency of 0.3. Here, hydrogen production is by 'direct' reduction of H^+ by $[RuL_3]^+$ over PtO_2 (reaction 74). Replacement of $[RuL_3]^{2+}$ by $[Ru(bipy)_3]^{2+}$ gave a quantum efficiency of 0.37. Hydrogen production using colloidal Pt has been reported.[177]

$$2[RuL_3]^+ + 2H^+ \xrightarrow{PtO_2} 2[RuL_3]^{2+} + H_2 \quad (74)$$

Other derivatives of $[Ru(bipy)_3]^{2+}$ have also been used in reductive cycles[178–180] and thus photolysis of aqueous solutions containing tris(2,2'-bipyrazinyl)Ru^{II} ($[RuL'_3]^{2+}$) or tris(2,2'-bipyrimidyl)Ru^{II} ($[RuL''_3]^{2+}$) with TEOA and MV^{2+} leads to formation of MV^+ with quantum yields of 0.77 and 0.44 respectively. These yields are increased to 0.98 and 0.85 if the solutions are degassed by freeze–pump–thaw cycles.[181] At first sight, these reactions would appear to proceed by the oxidative route described in Section 61.5.4.2.2 but comparison of k_q (MV^{2+}) and k_q (TEOA) reveals that a reductive mechanism operates with MV^{2+} being reduced by $[RuL'_3]^+$ or $[RuL''_3]^+$.

In conclusion, it should be noted that none of the systems described above has been coupled to an oxidative cycle for production of oxygen and it is difficult to see how this could be achieved.

61.5.4.3 Photoproduction of Hydrogen from Water Using Metalloporphyrin and Metallophthalocyanine Sensitizers

61.5.4.3.1 Photochemical properties

Metalloporphyrins and, to a lesser extent, metallophthalocyanines have attracted much interest as photosensitizers for water decomposition reactions. Their synthesis,[182–183] characterization[184] and properties[118] are well documented elsewhere and it is only intended here to discuss the photoproperties of direct relevance to water decomposition.

Porphyrins are highly coloured materials whose visible spectra exhibit two principle absorptions. The first is the so-called Soret or B band which is very intense and it usually found at about 420 nm — excitation at this wavelength gives rise to the second singlet excited state.[118] The second absorption is the Q band which is much less intense than the B band and is often accompanied by its weaker first vibrational overtone. The energy of this band can be used as a measure of the degree of interaction between the porphyrin π-system and the central metal ion.[185] The Q bands occur at longer wavelength than the B band.

Metallophthalocyanines, (MPc's) possess a very intense absorption at about 680 nm ($\varepsilon > 10^5$ dm^3 mol^{-1} cm^{-1}) which is blue shifted on complexation with third row transition elements. They can absorb a large fraction of the solar spectrum, but their potential application to hydrogen production is limited by their tendency to aggregate in solution[118] (although where the system allows, this aggregation can be prevented by the use of pyridine (5% w/w) or micelles).

Almost all photoreactions of porphyrins and phthalocyanines occur *via* the triplet state whose lifetime (*ca.* 1 ms at $T = 300$ K) and yields of formation are greatest for porphyrins. The redox potentials of porphyrins are also more amenable to water photoreduction *via* oxidative or reductive cycles and some selected values are found in Table 11.

Table 11 Redox Potentials[a] for Some Ground and Excited State Porphyrins and Phthalocyanines[118]

Compound	$\pi^0(P^+/P)$	$\pi^0(P/P^-)$	$\pi^0(P^+/P^*_T)$	$\pi^0(P^*_T/P^-)$
H_2TPP	+1.19	−0.81	−0.24	+0.62
ZnTPP	+0.78	−1.11	−0.70	+0.37
CdTPP	+0.87	−1.01	−0.67	+0.53
PdTPP	+1.26	−0.76	−0.53	+1.03
Pc	+1.34	−0.42	+0.10	+0.82
ZnPc	+0.92	−0.65	−0.21	+0.48

[a] Measured in eV *vs.* NHE. P^*_T denotes the triplet excited state.

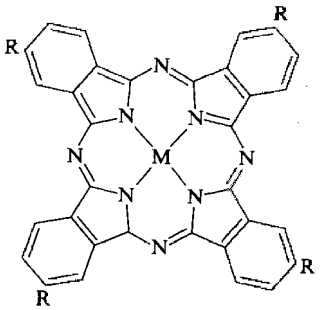
The coupling of these photochemical and redox properties to water reduction reactions is now described.

61.5.4.3.2 Metalloporphyrin sensitizers

Hydrogen producing systems employing metalloporphyrin sensitizers have usually consisted of the same components as systems employing $[Ru(bipy)_3]^{2+}$ as sensitizer, that is MV^{2+}, EDTA and colloidal Pt or hydrogenase. Whilst some reports have appeared[133,186-188] of hydrogen evolution employing water insoluble zinc *meso*-tetraphenylporphyrin (ZnTPP; Figure 6; R = Ph) in micelles or mixed organic/water systems, the bulk of the literature has centred on the water soluble analogues, tetra(*N*-methylpyridinium)porphyrinatozinc(II)($[ZnTMPyP]^{4+}$; Figure 6; R = py-Me$^+$) and zinc(II)tetra(4-sulfonatophenyl)porphyrinatozinc(II)($[ZnTSPP]^{4-}$; Figure 6; R = p-$C_6H_4SO_3^-$).

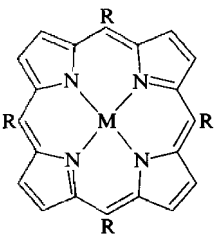
Hydrogen production from these latter compounds was demonstrated independently by Grätzel[189] and McLendon and Miller[190] in 1980.

On photolysis, $[ZnTMPyP]^{4+}$ is excited and rapidly intersystem crosses (with an efficiency of *ca.* 0.9) to the triplet state which has a lifetime of 1.3 ms. At $[ZnTMPyP]^{4+} = 10^{-5}$ mol dm^{-3} and $[MV^{2+}] = 5 \times 10^{-3}$ mol dm^{-3} this triplet state is oxidatively quenched with $k_q = 2 \times 10^6$ mol^{-1} dm^3 s^{-1}. However, at low $[MV^{2+}]$ and in the presence of EDTA (2×10^{-2} mol dm^{-3}) the triplet state can be reductively quenched with $k_q = 4 \times 10^5$ mol^{-1} dm^3 s^{-1}. Thus photolysis of solutions containing $[ZnTMPyP]^{4+}$, MV^{2+}, EDTA and Pt leads to hydrogen production and, in the light of the two possible quenching mechanisms, equations (75) to (82) were proposed.[189] At low $[MV^{2+}]$, a substantial amount of hydrogen is produced on photolysis, but reaction (77) occurs faster than reaction (76). This implies that reaction (81) occurs very much faster than reaction (80). In fact, reaction (76) only predominates at $[MV^{2+}] > 10^{-3}$ mol dm^{-3}. In the absence of EDTA and at $[Pt] = 8 \times 10^{-6}$ mol dm^{-3}, photolysis yields no hydrogen and leads to extensive destruction of the sensitizer, presumably by reduction to the dihydro- or tetrahydro-porphyrin. When [Pt] is raised to about 6×10^{-5} mol dm^{-3} however, hydrogen production is observed, presumably *via* reaction (83).[189] Thus, it is possible for hydrogen production to occur by parallel oxidative and reductive cycles.[189,190] Interestingly, McLendon and Miller[190] interpreted their findings in terms

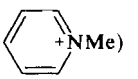


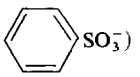
MPc (R = H)
$MPcTS^{4-}$ ($R = SO_3^-$)

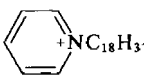
Metallophthalocyanines



MTPP (R = Ph)

$MTMPyP^{4+}$ (R= )

$MTSPP^{4-}$ (R= )

$MTOPyP^{4-}$ (R= )

Metalloporphyrins

Figure 6. Structures and nomenclature for metalloporphyrins and metallophthalocyanines

of a singlet state mechanism, but recent reports[118] indicate that as a result of spin selection rules, singlet quenching does not normally lead to redox products. Furthermore the short lifetime of the single excited state (*ca.* 10^{-9} s) would seem to preclude collisional encounter.

$$ZnTMPyP^{4+} \xrightarrow{h\nu} ZnTMPyP^{4+*} \quad (75)$$

$$ZnTMPyP^{4+*} + MV^{2+} \rightarrow ZnTMPyP^{5+} + MV^{+} \quad (76)$$

$$ZnTMPyP^{4+*} + EDTA \rightarrow ZnTMPyP^{3+} + EDTA^{+} \quad (77)$$

$$ZnTMPyP^{5+} + EDTA \rightarrow ZnTMPyP^{4+} + EDTA^{+} \quad (78)$$

$$EDTA^{+} \rightarrow H^{+} + EDTA\cdot \quad (79)$$

$$2ZnTMPyP^{3+} \rightarrow ZnTMPyP^{4+} + ZnTMPyP^{2+} \quad (80)$$

$$ZnTMPyP^{3+} + MV^{2+} \rightarrow ZnTMPyP^{4+} + MV^{+} \quad (81)$$

$$MV^{+} + H^{+} \xrightarrow{Pt} MV^{2+} + 0.5H_2 \quad (82)$$

$$ZnTMPyP^{3+} + H^{+} \xrightarrow{Pt} ZnTMPyP^{4+} + 0.5H_2 \quad (83)$$

Replacing $[ZnTMPyP]^{4+}$ by $[ZnTSPP]^{4-}$ also led to hydrogen evolution,[189,190] although the yields were substantially lower; in fact, the turnover number in the porphyrin dropped from 350 h^{-1} $[ZnTMPyP]^{4+}$ to 50 h^{-1} $[ZnTSPP]^{4-}$. Interestingly, these compare well with $[Ru(bipy)_3]^{2+}$ systems where the turnover under similar conditions is only 4 h^{-1}.[190]

The triplet excited state of $[ZnTSPP]^{4-}$ is oxidatively quenched by MV^{2+} with $k_q = 1.4 \times 10^{10}$ mol^{-1} dm^3 s^{-1}, and this high value is almost certainly due to static quenching arising from ground state complexation.[189] Despite the high rate of quenching, hydrogen production remains low and this is due to a low quantum yield of MV^{+} caused by electrostatic attraction between the redox products.

These findings were confirmed by Harriman *et al.*[191] who defined the optimum conditions for the reaction. In a solution buffered to pH 5 containing $[ZnTMPyP]^{4+}$ (2×10^{-5} mol dm^{-3}), MV^{2+} (8×10^{-3} mol dm^{-3}) EDTA, (1.5×10^{-3} mol dm^{-3}) and Pt (*ca.* 10^{-5} mol dm^{-3}), ϕ_{CE} (MV^{+}) was 0.75 and the quantum yield for hydrogen production was 0.3. This in fact represents 60% of the maximum possible efficiency for such a system. Irradiation of the same solution but omitting MV^{2+} gave a quantum yield for hydrogen production of 2×10^{-2} for the reductive cycle. However, whilst prolonged photolysis led to only minor bleaching of the chromophore, this bleaching was greater for the oxidative cycle. Thus exhaustive photolysis of the two systems gave approximately the same amount of hydrogen.[192]

More recent work by Richoux[193] showed that these efficiencies could be further increased, as the quantum yield for product ion formation on quenching of $[ZnTMPyP]^{4+*}$ by MV^{2+} increased

with temperature, whilst the rate of back electron transfer decreased. Interestingly, replacement of MV^{2+} by $C_{14}MV^{2+}$, gives cage escape yields of nearly 100%.[138]

Employing $[ZnTSPP]^{4-}$ as sensitizer and ascorbic acid as electron donor, Tabushi[194] also demonstrated photogeneration of hydrogen. Thus, irradiation of 8 cm^3 of a solution containing $[ZnTSPP]^{4-}$ (7×10^{-5} mol dm^{-3}), ascorbic acid (0.1 mol dm^{-3}), MV^{2+} (10^{-2} mol dm^{-3}) and Pt (1.1×10^{-4} mol dm^{-3}) at 0 °C yielded 100 μl (H_2) h^{-1}, with more than 99% of the chromophore and relay being unchanged after 9 h. On extended photolysis, the rate of hydrogen production decreased, and this was attributed to electron transfer from MV^{2+} to the dehydroascorbic acid produced. If MV^{2+} was left out of the reaction solution, then irradiation produced only 130 μl (H_2) in 3 h, by which time the chromophore was completely degraded. This was attributed to a demetallation of the porphyrin, which was confirmed by the observation that irradiation of a solution containing $[H_2TSPP]^{4-}$, ascorbic acid and Pt yielded the same amount of hydrogen. Replacement of MV^{2+} by hexylmethylviologen generated 7150 μl (H_2) in 10 h.[195]

$[ZnTSPP]^{4-}$ was shown to be an efficient photosensitizer in a system which did not require an electron relay.[196] Thus irradiation of 5 cm^3 of a solution containing $[ZnTSPP]^{4-}$ (4×10^{-4} mol dm^{-3}), TEOA (0.2 mol dm^{-3}) and platinized zinc oxide (Pt/ZnO 0.1–10 wt% Pt) gave hydrogen at a rate of 39.2 μl h^{-1} and a quantum yield of 0.03 (0.5 H_2). This system produced hydrogen *via* an oxidative cycle and was shown to be stable with no denaturation of the Pt/ZnO and negligible denaturation of the chromophore in 152 h.[196]

Whilst most of the above examples have been based on Zn chromophores, other metals have been investigated[118] and thus Sn^{IV},[197,198] Pd^{II},[199] Ru^{II}[200,201] and Cd^{II}[202] porphyrins have been shown to be capable of acting as effective chromophores and of these, the last has been found to be potentially superior to Zn.[202]

61.5.4.3.3 Metallophthalocyanine sensitizers

Despite their superior photoproperties, metallophthalocyanines[118,203] have not found use as photosensitizers for hydrogen production from water due to poor cage escape yields[204] and extensive ground state complexation by MV^{2+},[205] indeed MV^{2+} enhances the formation of phthalocyanine dimers. Thus, irradiation of solutions containing $[ZnPcTS]^{4-}$ (see Figure 6) EDTA and Pt produces hydrogen with quantum yields of $<10^{-4}$.

61.5.4.4 Redox Catalysts

Crucial to the success of reactions designed to produce hydrogen *via* intermolecular electron transfer reactions is the addition of an efficient redox catalyst which allows reduction of protons by the reduced form of the relay (*e.g.* MV^+) formed by the initial photochemical electron transfer.

Early studies relied on colloidal platinum or PtO_2,[127] although other metals, *e.g.* Rh and Pd,[206] have been employed. Ru, Au, Ir and Ag[206] are reported to be ineffective, although some authors have claimed H_2 production using a colloidal gold redox catalyst.[207] RuO_2 is active[136,208] for hydrogen production from MV^{2+} and has the added advantage that it does not catalyze the hydrogenation of MV^{2+} (see Section 61.5.4.2.2).

In general, the catalysts have been prepared by methods developed in the 1940s,[209] which involve reduction of H_2PtCl_6 or K_2PtCl_4 with, for example, citrate,[210] base[209] or $NaBH_4$[138,211] and can then be used directly, or, more usually, protected with a polymer, typically poly(vinyl alcohol)[209] carbowax 20M[138] or poly(vinylpyrrolidone),[212] a colloidal semiconductor such as TiO_2,[213–217] $SrTiO_3$,[218,186] ZnO[196] *etc.*, in zeolites or in cyclodextrins.[219] When unprotected, the catalysts tend to agglomerate giving them rather short active lifetimes.[220,221] An alternative synthesis involves radiolysis of solutions containing appropriate metal salts, *e.g.* H_2PtCl_6, and a water soluble acrylic monomer, *e.g.* acrylamide.[222] Radiolysis causes reduction of the salt with concomitant formation of polymer in which the colloidal metal particles (average dimeter *ca.* 17 Å) are trapped. Supported catalysts prepared in this way are indefinitely stable towards agglomeration.

The efficiency of the catalyst in the archetypal system, $EDTA/[Ru(bipy)_3]^{2+}/MV^{2+}/Pt$ is dependent upon its mode of preparation, its concentration, possibly the particle size, and the nature of the support.[219,223–226] Thus, unprotected colloids give lower rates of hydrogen production than those protected with PVA and most catalysts reach their maximum efficiency at [Pt] = $1–5 \times 10^5$ mol dm^{-3},[129,224,226,227] although for particles with diameters of *ca.* 30 Å (probably the most active particles), maximum rates are achieved at 2×10^{-6} mol dm^{-3}.[138] Under these conditions

it is probable that all of the MV^+ escapes back electron transfer and is intercepted by the Pt particles.

In systems where semiconductors are used to support the colloidal platinum, the electron transfer catalyst is often omitted and the primary electron transfer event involves injection of an electron from the excited state of the chromophore into the conduction band of the semiconductor.[196,216,217,228-230] Hydrogen production then occurs at the supported platinum particles. These systems are discussed in more detail in Section 61.5.4.6 but they can be highly efficient (quantum yields for hydrogen production up to 0.1)[229,230] and problems associated with relay hydrogenation are removed.

There is some dispute as to the importance of the size of the platinum particles in determining the rate of hydrogen production in the system $[Ru(bipy)_3]^{2+}/EDTA/MV^{2+}/Pt$ but most researchers suggest[213,219,226] that with PVA supported catalyst, the rate increases with decreasing catalyst size (at a given concentration) and then falls below *ca.* 20-30 Å.[211,212,219] The data available are rather limited and it has been shown[129] that particles of average diameter 16 Å are as effective as semi-aggregates of diameter 1000 Å. This may indeed by the case, but to assume that this implies no size dependence in between seems an over-simplification.[129] If indeed there were no size dependence, since measurements are made at constant catalyst concentration, it would be necessary to infer that each surface platinum atom were more active in the aggregates than in the smaller particles. It is more logical that the activity of the catalyst should be inversely proportional to the particle radius and, from the limited data available, this appears to be approximately the case (see Figure 7).[226]

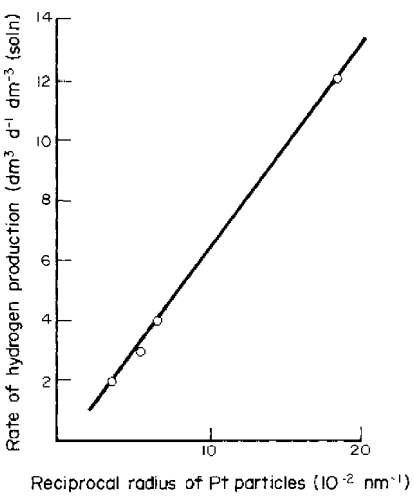


Figure 7. Variation of rate of hydrogen production with the reciprocal of the particle radius in the system, $[Ru(bipy)_3]^{2+}$ (4×10^{-5} mol dm^{-3}), MV^{2+} (10^{-3} mol dm^{-3}), EDTA (3×10^{-2} mol dm^{-3}), Pt protected with poly(vinyl alcohol) (1.4×10^{-2} mg dm^{-3}) (data taken from ref. 226).

The fall off in efficiency of the catalysts below 20-30 Å can probably be attributed either to problems associated with electron transfer to the particle or, more likely, to the inability of the small particles to accumulate sufficient electrons (or hydrogen radicals) to allow hydrogen production. The reaction specificity of the catalysts towards MV^+ oxidation may also be impaired.

Qualitatively, the role of the redox catalyst can be seen as a way of accumulating reducing equivalents. For platinum, uptake of an electron from, for example, MV^+ is immediately followed by protonation so that hydrogen radicals are effectively stored,[231] whereas for gold, protonation is much slower and the particle acts more as an electron store.[231] The surface of the particle may also allow specific orientation of the reducing agent so the hydrogen production at the remaining sites is easier.[232]

Quantitatively, the rate of hydrogen production is second order in [Pt] or [Au][232-234] and, although this has been attributed to particle-particle interactions,[232] it is found that, if the particles are considered as microelectrodes, spherical electrode kinetics will explain this behaviour, (at least for particles above 100 Å in diameter), whereas homogeneous reaction kinetics will not.[211,226,233,235-237]

At sufficiently high [Pt] the hydrogen-producing step has been reported[211,226,227] to be 100% efficient and not rate determining and it has been suggested that further work to improve the

efficiency of the catalyst is unnecessary.[227] However, this is not the case since ideally a platinum catalyst which was sufficiently active to compete with back electron transfer (so that all MV^+ underwent reaction 26 rather than 23), would allow hydrogen production and the accumulation of $[Ru(bipy)]^{3+}$ in the *absence* of a sacrificial electron donor and, since oxygen production from $[Ru(bipy)_3]^{3+}$ is possible (see Section 61.5.4.5), this would allow cyclic water cleavage.

For this objective to be realized, it is important that the platinum catalyst should react selectively with MV^+ and that it should not then transfer the electron back to the oxidized form of the sensitizer. Some rather elegant experiments towards this goal have been carried out.

Thus, using colloidal platinum protected by the positively charged polysoap poly(*N*-hexadecylvinylpyridinium bromide) and $C_{14}MV^{2+}$ as an electron relay, hydrogen can be produced[138] from either $[Ru(bipy)_3]^{2+}$ or $[Zn(TMPyP)]^{4+}$ in the absence of added reducing agent. The success of this reaction arises because $C_{14}MV^+$ interacts with the Pt particle in a manner similar to that in which it is incorporated into CTAC micelles (see Section 61.5.4.7.2) so that electron transfer to Pt is highly efficient, and because the oxidized form of the sensitizer is repelled from the platinum particle by the positively charged surface, hence preventing reduction of the oxidized form of the sensitizer by the reduced platinum particle.

Using a slightly different but related approach, it has been shown[203] that colloidal platinum supported by CTAC can selectively interact with reduced diheptylviologen (HV^+) and not allow back electron transfer to $[ZnTMPyP]^{5+}$ since this is electrostatically repelled from the reduced platinum particle by the surrounding CTAC molecules. Using the more hydrophilic MV^{2+}, the platinum particles cannot interact with MV^+ since it too is repelled by the positively charged surface. Unfortunately, in neither case is hydrogen produced on continuous photolysis. This may be because each platinum atom only accumulates a small number of electrons or because the surface coating increases the overpotential for hydrogen evolution.

Attempts to support colloidal platinum particles with surfactant zinc porphyrin micelles allow hydrogen production at lower platinum concentrations than when the porphyrin and the particle are separate but an irreversible electron donor is still necessary for hydrogen production.[116]

Finally, as an alternative to colloidal metal particles it is possible to use hydrogenase,[133,153,186,187,200,202,238–248] normally from *Desulphovibrio vulgaris*, or a synthetic analogue derived from Fe_4S_4 clusters[248] in the presence of bovine serum albumin, as the redox catalyst for production of hydrogen from MV^+ and protons.

Hydrogenase has comparable activity to colloidal platinum (although the direct comparison is difficult since the concentration of hydrogenase is usually unknown) and has the advantages of longer lifetime[221] (since agglomeration is not possible) and total homogeneity removing problems associated with light scattering. Its main disadvantages are its extraction, which requires skilled techniques and is time consuming, and its instability meaning that it must be stored at −196 °C.

61.5.4.5 Oxygen Production by Intermolecular Electron Transfer Processes

61.5.4.5.1 Uncatalyzed reactions

One of the major difficulties associated with catalytic photochemical water decomposition reactions is the requirement that four electrons be provided for each molecule of oxygen that is formed and there are very few compounds which allow this reaction to take place without the intermediacy of high energy species such as hydroxyl radicals. We therefore treat this subject in some detail.

Examination of equation (49) shows that this kind of reaction is in theory possible with $[Ru(bipy)_3]^{3+}$, and indeed it was the demonstration of oxygen production[105] from basic solutions of $[Ru(bipy)_3]^{3+}$ that spawned the enormous interest in the possible use of $[Ru(bipy)_3]^{2+}$ as a sensitizer for water decomposition. It had been known[249,250] for some time that $[M(bipy)_3]^{2+*}$, which is chemiluminescent, was generated on production of $[M(bipy)_3]^{3+}$ (M = Fe, Ru, Os) in basic solution[249–256] and that at least for $[FeL_3]^{3+}$ (L = bipy or phen), oxygen was produced.[252]* There was also some evidence that this reaction was accelerated by light.[251]

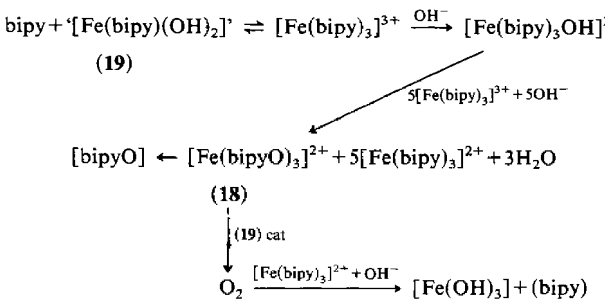
Initially it was believed[252] that hydroxyl radicals were the first formed products in these reactions but lack of any effect on the rate of the reaction by adding bromide, alcohols or benzene demonstrated that this was not the case. Furthermore, hydroxyl radicals react rapidly with $[Ru(bipy)_3]^{2+}$ to give a complex with $\lambda_{max} = 750$–800 nm which is similar to an intermediate in

* In acidic solution, different products can be obtained.[257]

the reaction between $[Ru(bipy)_3]^{3+}$ and OH^-. This suggests that OH^- bound to the metal or bipyridyl ligand might be being oxidized.[105]

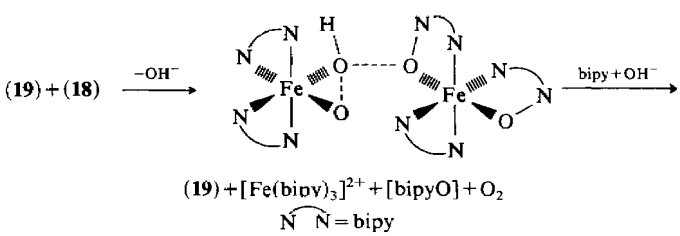
Highly complicated pH dependencies are observed for these reactions such that maximum O_2 yields are obtained at pH 9 for M = Ru (80%)[105] and 13 for M = Fe (70%).[258] One report[259] suggests that O_2 can be produced at pH 1 from $[Ru(bipy)_3]^{3+}$ in an uncatalyzed reaction. For M = Os, however, oxygen is evidently not produced, and more recently it has been suggested by a number of workers,[260–264] that in the absence of catalysts O_2 is not produced from any of these species. Reduction of M^{3+} does occur, however, the reducing agent being bipyridyl, which can be oxidized to CO_2.[262] There is some evidence to suggest that photochemically excited $[Ru(bipy)_3]^{3+}$ *does* oxidize water to oxygen in the absence of added catalysts.[265]

Recent studies[261] of the $[Fe(bipy)_3]^{3+}$ system have shown that, although O_2 is produced from $[Fe(bipy)_3]^{3+}$ in basic aqueous solution, it is *only* formed if dissociation of bipyridyl occurs. The much lower yields of O_2 obtained from $[Fe(phen)_3]^{3+}$ can then be attributed to the lower lability of this complex. The complex formed on dissociation of bipyridyl is believed to be $[Fe(bipy)_2(OH)_2]^{2+}$ (**19**) or possibly the oxo-bridged dimer $[Fe(bipy)_2O]_2^{4+}$, which can be formed from $[Fe(bipy)_3]^{n+}$ ($n = 2$ or 3), and which is known to catalyze O_2 production from water.[266] Although these Fe^{IV} complexes do not themselves produce oxygen from water, it is believed[261,266] that they catalyze the production of oxygen from the bipyridyl *N*-oxide (bipyO) complex $[Fe(bipyO)_3]^{2+}$ (**18**), which in turn is formed along with $[Fe(bipy)_3]^{2+}$ from $[Fe(bipy)_3]^{3+}$, OH^- and $[Fe(bipy)_3OH]^{2+}$ (see Scheme 3). The exact nature of this last mentioned hydroxo intermediate is unclear. It may be an ion pair or it may be formed by attack of OH^- on the metal, a nitrogen atom or a carbon atom of the bipy group. Attack on C would appear to be eliminated by the observation that bipyO is a reaction product. It has been suggested[267] that attack on the metal leads to O_2 production, whilst attack on the ligand, which is favoured by electrophilic substituents, leads to ligand hydroxylation. Perhaps electron donating substituents would lead to higher yields of O_2. A discussion of the reactions of metal bipyridyl complexes with water and hydroxide ions appears elsewhere in these volumes.



Scheme 3 Mechanism of 'uncatalyzed' formation of O_2 from $[Fe(bipy)_3]^{2+}$ [261]

The release of oxygen from $[Fe(bipy)_3]^{3+}$ is believed to occur as shown in Schemes 3 and 4 and does not involve high energy radical intermediates.[261] The first step, attack of hydroxide ion on $[Fe(bipy)_3]^{3+}$, is generally accepted as[105,258,261] being rate determining but other workers have concluded[250] that Fe^{IV} intermediates of the form $[Fe(OH)(bipy)_3]^{3+}$ produce hydrogen peroxide by reaction with OH^- and that $[Fe(bipy)_3]^{3+}$ oxidizes H_2O_2 to O_2. Evidence for these intermediates is lacking, although it has been reported that H_2O_2 can sometimes be detected as a product.[254] This result has recently been questioned.[268]



Scheme 4 Mechanism of oxygen formation from $[Fe(bipyO)_3]^{2+}$ [261]

As far as ruthenium is concerned, a number of unidentified ruthenium containing products are obtained[105] in small amounts during the reaction of $[Ru(bipy)_3]^{3+}$ with OH^-. These could be compounds such as $[Ru(bipy)_3O]^{2+}$ (with monodentate bipyridyl[269]), $[\{Ru(bipy)_2(H_2O)\}_2O]^{4+}$ [270]

or even *cis*-$[Ru(bipy)_2(H_2O)_2]^{2+}$,[270] all of which (or close analogues) have been shown to be active catalysts for water oxidation by oxidizing agents such as Ce^{4+} or even $[Ru(bipy)_3]^{3+}$.[270]

The available evidence clearly indicates that little or no oxygen is produced in the uncatalyzed reaction of $[M(bipy)_3]^{3+}$ with OH^- and that small amounts of decomposition lead to adventitious catalysts for oxygen evolution. It is hardly surprising therefore that considerably more efficient O_2 generation is observed if catalysts are added.

61.5.4.5.2 Homogeneous catalysts for oxygen production

Hexaaqua ions of a large number of transition metals, *e.g.* Mn^{II}[271] Cu^{II}, Co^{II}, Fe^{II}, Fe^{III} and Ni^{II},[262,272] catalyze the production of oxygen from $[M(bipy)_3]^{3+}$ (M = Ru, Os or Fe) and one electron oxidizing agents such as $[IrCl_6]^{2-}$ and $[Co(H_2O)_6]^{3+}$ over a wide pH range. Yields up to 75% of O_2 are obtained from $[Ru(bipy)_3]^{3+}$ catalyzed by Co^{II} at pH 6–12 and yields of decomposition products containing Ru are much lower than for the uncatalyzed reaction.[273,274] The kinetics of this reaction at pH 7 are highly complex but can be interpreted[263,274] in terms of rate determining formation of a cobalt(IV) intermediate which oxidizes water to H_2O_2 followed by oxidation of H_2O_2 by $[Ru(bipy)_3]^{3+}$ (see equations 84–88). Unfortunately, reaction (89) causes loss of cobalt as an insoluble oxide and this accounts for the observed decrease of catalytic activity with time.

$$Co^{2+} + 2H_2O \rightleftharpoons Co(OH)_2 + 2H^+ \quad (84)$$

$$Co(OH)_2 + [Ru(bipy)_3]^{3+} \rightleftharpoons [Co(OH)_2]^+ + [Ru(bipy)_3]^{2+} \quad (85)$$

$$[Co(OH)_2]^+ + [Ru(bipy)_3]^{3+} \xrightarrow{slow} [CoO]^{2+} + [Ru(bipy)_3]^{2+} + H_2O \quad (86)$$

$$[CoO]^{2+} \rightarrow Co^{2+} + H_2O_2 \quad (87)$$

$$2[Ru(bipy)_3]^{3+} + H_2O_2 \rightarrow [Ru(bipy)_3]^{2+} + O_2 + 2H^+ \quad (88)$$

$$[CoO]^{2+} + Co^{2+} \rightarrow [CoOCo]^{4+} \rightarrow \text{ppt} \quad (89)$$

For manganese, a slightly different mechanism involving formation of $[MnO_4]^-$ and MnO_2, presumably *via* oxidation to $[MnO_4]^{2-}$ and disproportionation, has been suggested[271] and oxygen is then formed by the known oxidation of water by $[MnO_4]^-$ catalyzed by MnO_2. A similar mechanism accounts for the catalysis of O_2 production from PbO_2 and water by Mn^{II},[275] as well as for O_2 production from Ce^{4+} catalyzed by MnO_2 or Co_2O_3.[276]

Complexes of similar metals with other ligands such as bipy, ammonia, and 1,2-diaminoethane[277] are also catalytically active for oxygen production from $[Ru(bipy)_3]^{3+}$ but it is believed that partially hydrolyzed forms are the active species. Many of these complexes are more active oxygen evolving catalysts than the parent hydrated species and it has been concluded that *cis*-diaqua complexes which can dimerize to di-μ-hydroxo forms are the active species.[277] Since considerable activity is observed at pH < 5, where on account of the redox potentials of $[Ru(bipy)_3]^{3+/2+}$ (1.26 V) and H_2O_2/H_2O (1.4 V), equilibrium concentrations of H_2O_2 can only be 10^{-6}–10^{-7} mol dm^{-3}, it is concluded that genuine four-electron oxidation of H_2O to O_2 occurs, perhaps by a reaction such as (90) involving a dioxo bridged intermediate. The most active species appear to be those containing Co and Fe.

$$2[CoO]^{2+} \rightarrow 2Co^{2+} + O_2 \quad (90)$$

Similarly, using phthalocyanine or porphyrin complexes of a range of transition elements, cobalt and iron again appear[278] to be the best metal ions. Although the mechanisms of the reactions are not fully understood, it is believed that two-electron oxidation is again important and some correlation between oxygen yield and redox potential (M^{3+}/M^{2+}) for the phthalocyanine complexes is observed. The anomalously low efficiency of zinc compounds compared with those of cobalt, which have similar first oxidation potentials, suggests that the second oxidation potentials are also important.[278]

The catalytic photochemical oxidation of water can also be achieved[272,279] by similar methods, for example photolysis of $[Ru(bipy)_3]^{2+}$ using $[Co(NH_3)_5Cl]^{2+}$ as a sacrificial electron acceptor. The quantum yield for O_2 production is *ca.* 0.025[272] in the absence of added redox catalyst, although this result has been questioned.[280,281]

The mechanism of this photochemical reaction is as shown in equations (91)–(94) and relies upon oxidative quenching of $[Ru(bipy)_3]^{2+*}$ by the cobalt complex to give $[Ru(bipy)_3]^{3+}$ and highly labile cobalt(II) amine complexes which decompose at a rate which competes with back

electron transfer to yield much more weakly reducing aquacobalt(II) complexes. The $[Ru(bipy)_3]^{3+}$ then oxidizes water either in the presence of an added Co^{2+} catalyst[279,280] (Fe^{II}, Co^{II}, Ni^{II} or preferably insoluble Co^{III} or Fe^{III} hydroxides if $[S_2O_8]^{2-}$ is used as acceptor)[273] or relying upon the cobalt(II) complexes formed from $[Co(NH_3)_5Cl]^{2+}$ in the photochemical reaction.[272]

$$[Ru(bipy)_3]^{2+} \xrightarrow{h\nu} [Ru(bipy)_3]^{2+*} \quad (91)$$

$$[Ru(bipy)_3]^{2+*} + [Co(NH_3)_5Cl]^{2+} \rightarrow [Ru(bipy)_3]^{3+} + [Co(NH_3)_5Cl]^{+} \quad (92)$$

$$[Co(NH_3)_5Cl]^{+} + 6H_2O \rightarrow [Co(H_2O)_6]^{2+} + 5NH_3 + Cl^{-} \quad (93)$$

$$[Ru(bipy)_3]^{3+} + OH^{-} \xrightarrow{cat} [Ru(bipy)_3]^{2+} + 0.25O_2 + 0.5H_2O \quad (94)$$

Efficient O_2 production is observed over a narrow pH range (4–6) and it is probable that both the rate of oxygen production and the yield maximize at pH 5.[280] It is also found that the dependence on added $[Co^{2+}]$ is complicated, the rate maximizing at $\sim 10^{-4}$ mol dm^{-3}, whilst the O_2 yield decreases as $[Co^{2+}]$ increases.[272,280]

This photochemical reaction, as well as O_2 production from PbO_2, can also be catalyzed[282,283] by $[Ru(bipy)_2(H_2O)_2]^{2+}$ in free solution or with all the components adsorbed onto hectorite at pH values down to 1. The independence[283] of the rate of O_2 production upon pH (Figure 8) is remarkable and suggests that catalytic oxygen generation itself is not rate determining but rather that the rate limiting step is some physical process such as ion transport, cage recombination, *etc.*

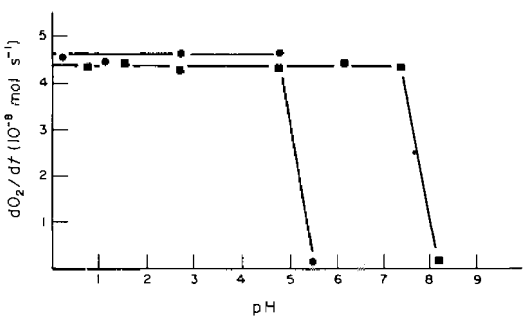


Figure 8. pH dependence of the initial oxygen evolution rate in the following photochemical test system: (■) 50 ml of $[Co(NH_3)_5Cl]^{2+}$ saturated H_2O, 100 mg of hectorite 10% of the cations of the clay exchanged with $[Ru(bipy)_2]^{2+}$ and 10% exchanged with $[Ru(bipy)_2(H_2O)_2]^{2+}$; (●) same total concentrations, but in a purely homogeneous medium (reproduced from ref. 283)

The active isomer of the Ru complex is believed to be *cis* despite the fact that it isomerizes to *trans* on adsorption on the clay minerals.[283] It is believed that the isomerization does not occur with 100% yield and that the small amount of unisomerized *cis*-$[Ru(bipy)_2(H_2O)_2]^{2+}$ is responsible for the observed catalytic activity. This is supported by the observation that reactions starting from *trans*-$[Ru(bipy)_2(H_2O)_2]^{2+}$ do not produce O_2.

Once again, the overall reaction is believed to involve two-electron oxidations to a ruthenium(IV) oxo species but in this case oxidation to a monomeric dioxoruthenium(IV) intermediate apparently takes place. Loss of O_2 occurs *via* a peroxo intermediate (equations 95–98, equation 96 occurs stepwise).[283] The need for the *cis* isomer is then obvious. Unfortunately, catalyst instability (only about 30 electrons can be transferred per molecule) means that this interesting system is not suitable for commercial exploitation.[283]

$$[Ru(bipy)_3]^{3+} + cis\text{-}[Ru(bipy)_2(H_2O)_2]^{2+} \rightarrow [Ru(bipy)_3]^{2+} + H^{+} + cis\text{-}[Ru(bipy)_2(OH)(OH_2)]^{2+} \quad (95)$$

$$cis\text{-}[Ru(bipy)_2(OH)(OH_2)]^{2+} + 3[Ru(bipy)_3]^{3+} \rightarrow cis\text{-}[Ru(O)_2(bipy)_2]^{2+} \quad (96)$$

$$cis\text{-}[Ru(O)_2(bipy)_2]^{2+} \rightarrow [Ru(O_2)(bipy)_2]^{2+} \quad (97)$$

$$[Ru(O_2)(bipy)_2]^{2+} + 2H_2O \rightarrow [Ru(bipy)_2(H_2O)_2]^{2+} + O_2 \quad (98)$$

One other interesting aspect of this[283] and related[279] systems is that dinitrogen is a product. It is apparently formed *via* catalytic oxidation of NH_3 or NH_4^+ which are released by the rapid solvolysis of $[Co(NH_3)_5Cl]^{+}$.

The crucial importance of the use of an irreversible electron acceptor for oxygen production in these photochemical systems is demonstated by the observation that replacing $[Co(NH_3)_5Cl]^{2+}$ by Fe^{3+} causes the yield of O_2 to drop to zero,[280] presumably because back electron transfer

competes with OH^- oxidation, even if the most active redox catalysts are employed. The one exception to this general observation is that at *high pH* (7–13.5) photolysis of solutions containing only $[Ru(bipy)_3]^{2+}$ and MV^{2+} leads[284–286] to the catalytic formation of MV^+ with an initial quantum yield of 0.029.[286] Since MV^{2+} is an efficient quencher of $[Ru(bipy)_3]^{2+*}$, it is probable that the mechanism of this interesting reaction is as in equations (21), (22) and (49) and the reaction of $[Ru(bipy)_3]^{3+}$ with OH^- must compete with back electron transfer to MV^+. The exact fate of the $[Ru(bipy)_3]^{3+}$ is unknown except that $[Ru(bipy)_3]^{2+}$ is regenerated. It has been suggested that O_2 is produced but in view of the discussion above, it is perhaps more likely that a small amount of ligand oxidation occurs. It would seem that attempts to carry out this reaction in the presence of O_2 producing catalysts would be highly beneficial.

The importance of this reaction lies in the fact that MV^+ is efficient for *hydrogen* evolution in the presence of suitable catalysts but only at $pH < 5$; furthermore, neutralization of the post irradiated solution *does* produce H_2.[285] Although this system itself does not allow both H_2 and O_2 production on account of conflicting pH requirements, it does suggest various ways forward towards cyclic water cleavage. These include: (a) the use of electron transfer catalysts which have sufficient reducing power to reduce water at high pH; (b) the possibility of using a neutral electron transfer catalyst to transfer electrons across a membrane which separates solutions of low and high pH — such a system would have the added advantage that O_2 and H_2 production would be separated but the disadvantage that H^+ and OH^- rather than H_2O would be consumed; or (c) the use of a photochemical cell in which the anode and cathode compartments are at high and low pH respectively.

61.5.4.5.3 Heterogeneous catalysts for oxygen production

(i) Unsupported metal oxides

None of the homogeneous catalysts discussed above has proved suitable for use in cyclic water cleavage and few of them operate at low pH, where hydrogen production is favoured. The real breakthrough from both of these points of view occurred when it was shown[287] that colloidal PtO_2 or IrO_2 can catalyze the production of oxygen from one-electron oxidants such as Ce^{4+} or, more importantly for water decomposition, from $[Ru(bipy)_3]^{3+}$ at pH values as low as 1. Subsequent studies showed that RuO_2 or colloidal ruthenium (which is probably a colloid consisting of ruthenium covered with a layer of RuO_2) supported by poly(vinyl alcohol) were even more efficient for O_2 production from Ce^{4+},[34,288] $[Ru(bipy)_3]^{3+}$,[34,281] or PbO_2.[289] Colloidal dispersions were *ca.* 100 times as active as powders.[288]

The original results concerning the reaction with Ce^{4+} were questioned[290] and it was suggested that RuO_2 was oxidized to RuO_4, which did not decompose to RuO_2 and O_2 under the reaction conditions. However, it was subsequently pointed out[291] that the ratio of Ce^{4+}/RuO_2 is crucial to the success of the reaction. At high catalyst concentrations and surface areas, the electrochemical potential of the RuO_2 particle is quite low and oxygen production is favoured over RuO_2 corrosion, whereas if only small amounts of RuO_2 are employed, RuO_4 production will be the major reaction. Similar electrochemical arguments have been used to rationalize[291] the observed decrease in oxygen yield with $[Ce^{4+}]$ at high $[RuO_2]$.

Using $[Ru(bipy)_3]^{3+}$ as oxidizing agent in thermal or photochemical reactions, adsorbed Ru^{VIII} species have also been proposed[292] to be formed from RuO_2. These can lead to RuO_4, water oxidation or ligand oxidation to CO_2. That Ru^{VIII} intermediates are probably important has been elegantly demonstrated[292] by the observation that the pH at which O_2 production begins for $[M(bipy)_3]^{3+}$ (M = Fe, Os or Ru) correlates well with the pH at which RuO_4 becomes capable of being generated from RuO_2 by $[M(bipy)_3]^{3+}$. Furthermore, water is then oxidized directly by RuO_4 in a tetra-electronic step rather than *via* H_2O_2, which is thermodynamically inaccessible (see Figure 9). These results also hold if $[Ru(bipy)_3]^{3+}$ is photogenerated from $[Ru(bipy)_3]^{2+}$ with $[S_2O_8]^{2-}$ or $[Co(NH_3)_5Cl]^{2+}$ as sacrificial electron donors, and higher rates of oxygen production are apparently observed.[292] This may be because photoexcited $[Ru(bipy)_3]^{3+}$ is the water oxidant.[265]

RuO_2 supported by polybrene increases the rate of reduction of $[Ru(bipy)_3]^{3+}$ by two orders of magnitude and the rate increases with increasing pH from 1 to 10 and increasing RuO_2 concentration.[293] Care should, however, be taken in interpreting these results since the rate of formation of $[Ru(bipy)_3]^{2+}$ rather than O_2 was measured. Other workers have shown[262] that O_2 production in a similar system maximizes at pH 4 and does not occur above pH 7.

Similar problems have been noted for $[Fe(bipy)_3]^{3+}$ in the oxidation of water catalyzed by RuO_2 in that at pH 4 no O_2 is observed but a product which has a similar visible spectrum to

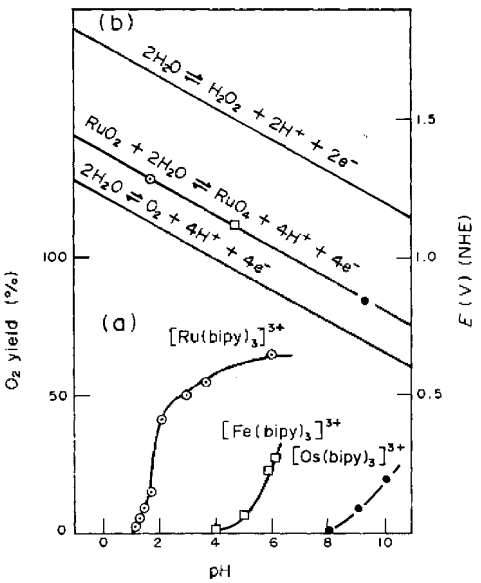


Figure 9. (a) O_2 yields as a function of pH in water oxidation with $[M(bipy)_3]^{3+}$(10^{-3} mol dm^{-3}) complexes in the presence of RuO_2 catalyst (10^{-4} mol dm^{-3}). (b) E-pH diagram for water oxidation, RuO_4 reduction and redox potentials of tris(bipyridine) complexes (⊙, $[Ru(bipy)_3]^{3+/2+}$; □, $[Fe(bipy)_3]^{3+/2+}$; ●, $[Os(bipy)_3]^{3+/2+}$) (reproduced from ref. 292)

$[Fe(bipy)_3]^{2+}$ is obtained. Interestingly, neutralization of this solution produces O_2 and gives authentic $[Fe(bipy)_3]^{2+}$.[294] The onset of oxygen production in these systems is at *ca.* pH 4[289,292,294] with both O_2 yield[289,294] and the rate of O_2[295] production maximizing at *ca.* pH 9 (pH 7 for powdered RuO_2).[294] The rate of oxygen production is approximately first order in catalyst concentration.[289,295]

Of the oxidants described above, only $[Ru(bipy)_3]^{3+}$ can be efficiently prepared in a photochemical reaction and hence has potential for use in a cyclic water cleavage system. Many studies have, thus, been carried out on the RuO_2 catalysis of O_2 production from $[Ru(bipy)_3]^{3+}$ generated photochemically from $[Ru(bipy)_3]^{2+}$ and a sacrificial electron acceptor such as $[Co(NH_3)_5Cl]^{2+}$ or $[S_2O_8]^{2-}$.

Initial studies suggested[281] that oxygen production occurred at pH 1.4 but that it was considerably faster at pH 4.9. Other colloidal metal oxides also catalyzed the reaction. Labelling studies confirmed that O_2 was derived from water[260,281] but examination of the relative yields of Co^{2+} and O_2 when using $[Co(NH_3)_5Cl]^{2+}$ as acceptor, suggest that only about 20% of the $[Ru(bipy)_3]^{3+}$ generated produces O_2 oxidatively.[279] Similar results have been suggested[280] by quantum yield studies using RuO_2/TiO_2 as catalyst, which show that although the quantum yield for $[Ru(bipy)_3]^{2+}$ formation is 0.3, that for O_2 formation is only 0.03 (for a stoichiometric reaction, a value of *ca.* 0.075 would be expected). This discrepancy almost certainly arises[279] from the concomitant oxidation of NH_3 or NH_4^+ in the system to N_2 as well as from a small amount of deep ligand oxidation of bipyridyl. This, perhaps, explains why better O_2 yields can be obtained in the dark from $[Ru(bipy)_3]^{3+}$ (see above) or using other irreversible donors such as PbO_2, although in the last reaction, significant uncatalyzed O_2 production also occurs.[260]

In many of the reactions catalyzed by RuO_2, reproducibility has been a problem,[280] although it is apparently improved by using colloidal RuO_2. (Non-hydrated RuO_2 is not catalytically active.[294]) Early experiments were carried out with RuO_2 (or Ru) derived from $RuCl_3$[288] but colloidal RuO_2 is preferably prepared from RuO_4 by stirring with a polymer support, *e.g.* styrene-maleic anhydride copolymer (SMA), at pH 9 when spontaneous RuO_2 production occurs.[294] Alternatively $KRuO_4$[292] (which is more easily purified than RuO_4) can be reduced with H_2O_2[292] or in boiling base[289] to an RuO_2 colloid which can be stabilized by sodium dodecylsulfate (SDS) or poly(vinyl alcohol).[289] Such stabilized RuO_2 colloids have radii of ~90 nm and shelf lives of over six months[289] compared with 30 nm and less than one month for more conventional colloids.[295] Typical first order rate constants for the oxidation of water by $[Fe(bipy)_3]^{3+}$ are ~0.4 s^{-1} at pH 7 for the SDS protected colloid[234] and ~0.04 s^{-1} at pH 9 for the SMA protected colloid.[295]

Somewhat similar results to those obtained with RuO_2 have been obtained using MnO_2[296] in the photochemical system employing $[Co(NH_3)_5Cl]^{2+}$ as sacrificial electron acceptor. Thus, the

rate of O_2 production increases to $[MnO_2]$ of 8.6 mol dm^{-3} and then drops slightly, presumably because of light absorption and scattering. The maximum O_2 yield is observed at pH 3.6. This appears to be due to the fact that, although the initial rate of O_2 production increases from pH 3.6, at higher pH, O_2 is only generated for a short time (30 min at pH 4.9 and 6 min at pH 6.0). Apparently only activated β-MnO_2 catalyzes O_2 production efficiently.[296]

(ii) Supported metal oxide and related catalysts

The low reproducibility of certain of the systems involving heterogeneous catalysts, described above, as well as the potential for charge separation using semiconductor catalysts has led to the use of heterogeneous catalysts supported on semiconducting materials, *e.g.* TiO_2.

These supported catalysts are generally synthesized[218,297] from commercial or specially prepared TiO_2 particles by stirring with $RuCl_3$ at pH 4–6, filtering and drying at 100 °C. Catalysts prepared in this way are at least an order of magnitude more efficient for O_2 production than powdered RuO_2[280] or than those where RuO_2 is incorporated into the body of the TiO_2 particle at the time of its preparation from, *e.g.* $TiCl_4$.[298] Alternatively, the RuO_2 can be deposited from $[Ru_3(CO)_{12}]$[299] or RuO_4[300,301] and may be polymer protected.[301]

Typical particle diameters are of the order of 20 nm[302] and, as with unsupported RuO_2, the hydrate, $RuO_2 \cdot 3.6H_2O$ is apparently the active species.[303]

In general, $[S_2O_8]^{2-}$ has been used[218,302,303] as the sacrificial electron donor in photochemical oxidation of water sensitized by $[Ru(bipy)_3]^{2+}$. This has certain advantages since $[Ru(bipy)_3]^{3+}$ is formed with a quantum yield of 2 according to equations (99)–(101). However, this system has certain disadvantages since substantial loss of chromophore occurs on prolonged photolysis, and there is some suspicion[280] that O_2 may be formed without the intermediacy of $[Ru(bipy)_3]^{3+}$. Although it is generally accepted that in the absence of sensitizer $[S_2O_8]^{2-}$ and RuO_2/TiO_2 do not produce oxygen with appreciable rates in the dark or on irradiation, no data are available on the reaction of $[SO_4]^{-}$ formed in equation (100) with water in the presence of RuO_2/TiO_2, and it is at least possible that O_2 may be produced from this reaction.

$$[Ru(bipy)_3]^{2+} \xrightarrow{h\nu} [Ru(bipy)_3]^{2+*} \tag{99}$$

$$[Ru(bipy)_3]^{2+*} + [S_2O_8]^{2-} \rightarrow [Ru(bipy)_3]^{3+} + [SO_4]^{2-} + [SO_4]^{-} \tag{100}$$

$$[Ru(bipy)_3]^{2+} + [SO_4]^{-} \rightarrow [Ru(bipy)_3]^{3+} + [SO_4]^{2-} \tag{101}$$

Nevertheless, $[S_2O_8]^{2-}$ provides a useful electron acceptor which, unlike $[Co(NH_3)_5Cl]^{2+}$, does not cause such large changes in the pH of the solution consequent upon its rapid decomposition after reduction. This has allowed combined studies of conductance and absorbance of solutions obtained[302] in flash photolysis experiments to prove that O_2 is liberated at the same rate as that with which $[Ru(bipy)_3]^{3+}$ decays and hence to show that RuO_2 does not 'collect holes' but rather passes them directly to a water molecule or, more likely, to an OH^-. The rate determining step at low catalyst loadings or concentrations using $[Co(NH_3)_5Cl]^{2+}$[280] or $[S_2O_8]^{2-}$[298,302,303] is probably diffusional encounter of $[Ru(bipy)_3]^{3+}$ with TiO_2/RuO_2 particles and this is thought[302] to have a second order rate constant as high as 5×10^{10} mol^{-1} dm^3 s^{-1}, which is very close to the diffusion controlled limit. At higher catalyst loadings (>2.5% RuO_2[302,303] or 10% if RuO_2 is incorporated into the body of the particles[298]), this step is no longer rate determining and the rate can even drop slightly.[298,303] This reduction of rate at higher catalyst loadings, which is also usually observed[298,303] at higher concentrations of catalysts with a given loading, has been attributed to light absorption by the RuO_2 leading to a lower overall light intensity for absorption by the chromophore. Consistent with this explanation are the observations that: (a) the rate of oxygen evolution is proportional to incident light intensity,[303] and (b) in non-photochemical systems such a fall off is not observed at higher catalyst loadings.[303] In these cases O_2 evolution increases[303,304] with increasing RuO_2 coverage up to *ca.* 7% and then levels off. This levelling off is generally assumed to arise because at these high coverages, the catalyst is so efficient for electron transfer that this electron transfer step is no longer rate determining.[280,300,304]

However, very recently it has been shown[304] that the total yield of O_2 from Ce^{4+} catalyzed by RuO_2/TiO_2 (under irradiation?) increases up to an RuO_2 loading of *ca.* 6% and then falls slightly. Interestingly, the magnetic susceptibility per gram of RuO_2/TiO_2 for the particles shows exactly analogous behaviour (see Figure 10). This suggests that paramagnetic particles are required for the O_2 producing reaction and that at higher coverages, antiferromagnetic coupling between particles occurs to give lower magnetic moments.[304] These coupled particles may then be more susceptible to corrosion to RuO_4, accounting for the lower O_2 yields.

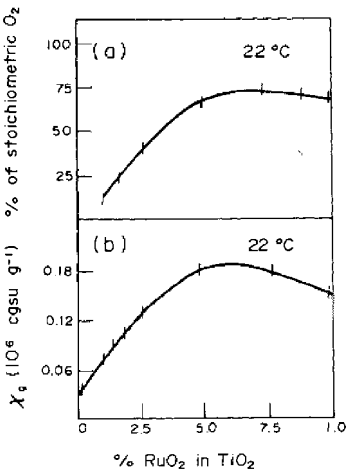


Figure 10. (a) Evolution as percentage of stoichiometric O_2 from Ce^{4+} and H_2O as a function of RuO_2 loading on TiO_2. (b) Variation with composition of the magnetic susceptibility per gram (χ_g) of RuO_2/TiO_2 as a function of RuO_2 loading on TiO_2 (reproduced from ref. 304)

The photochemical oxygen producing reactions are sensitive to pH, the rate constant for O_2 production increasing by two orders of magnitude from pH 4–7.[302]

Broadly similar conclusions have been reached using non-photochemically generated $[Ru(bipy)_3]^{3+}$[293] or Ce^{4+} as electron acceptors, although no rate reduction is observed at higher catalyst loadings or catalyst concentrations. With $[Ru(bipy)_3]^{3+}$, the rate of reaction can be increased[293] by 2–3 orders of magnitude compared with the uncatalyzed reaction and particular advantages are observed at pH 2–6, although the maximum absolute rates are obtained at pH 8–10. It should be noted, however, that these results refer to $[Ru(bipy)_3]^{3+}$ decay — O_2 production was not measured.[293]

Because of their relationship to chlorophyll, metalloporphyrins have received considerable attention in water splitting systems. Success has been achieved in hydrogen production using sacrificial systems (see Section 61.5.4.3.2) but there is only one report of O_2 production.[94] Using Fe^{3+} or Ag^+ as reversible electron donors, $[ZnTMPyP]^{4+}$ produces O_2 on photolysis in the presence of RuO_2/TiO_2. Maximum rates of O_2 production are observed at 1% RuO_2 loading and above, and at pH 1.6 (Fe^{3+}) or 4.5 (Ag^+). The rate using Fe^{3+} as acceptor drops by a factor of 5 at pH 2.5 or 0.8, the latter because of substantial demetallation of the porphyrin. The mechanism of this reaction may involve quenching of $[ZnTMPyP]^{4+}$ by Fe^{3+} and catalysis of the production of O_2 by the RuO_2/TiO_2 from the subsequently formed $[ZnTMPyP]^{5+}$. At first sight, it would appear that the efficiency of the catalyst must be exceptional since Fe^{3+}/Fe^{2+} is a reversible couple and back electron transfer is extremely rapid,[280] at least from $[Ru(bipy)_3]^{3+}$. However, using the more highly charged $[ZnTMPyP]^{4+}$, flash photolysis studies suggest that Fe^{2+} *can* be formed in high quantum yields from Fe^{3+} at low pH and in the absence of a catalyst. Thus, RuO_2/TiO_2 should be able to intercept $[ZnTMPyP]^{5+}$ before it can back react with Fe^{2+}. The alternative, and perhaps more likely, explanation involves injection of an electron from the excited state of the sensitizer into the conduction band of the TiO_2. Charge separation then occurs at the semiconductor surface and $[ZnTMPyP]^{5+}$ oxidizes H_2O as before. The back electron transfer from Fe^{2+} is less likely in this case since Fe^{2+} is generated by the injected electron at a site remote from the formation of $[ZnTMPyP]^{5+}$.[94] In the absence of a redox catalyst, O_2 is not produced even if $[S_2O_8]^{2-}$ is employed as electron donor.[305]

More seriously, other workers have been unable to observe[306] O_2 production from identical systems using RuO_2/TiO_2 as redox catalyst. A wide range of donors, pH and RuO_2/TiO_2 preparations was employed but oxygen could not be detected as a product on photolysis even though: (a) flash photolysis studies showed that $[ZnTMPyP]^{5+}$ was formed, although its lifetime was short and it probably disproportionated or was further oxidized to $[ZnTMPyP]^{6+}$, and (b) oxygen production *was* observed using the same catalysts and $[Co(NH_3)_5Cl]^{2+}$ but $[Ru(bipy)_3]^{2+}$ as chromophore.[306] Furthermore, oxygen production using $[ZnTMPyP]^{4+}$ was not observed even using RuO_2/TiO_2 provided by the group that had previously been successful in observing O_2 production.[94] The initial observations of oxygen production using this catalytic system must therefore, be viewed with some suspicion.

Other porphyrins which undergo[306] photooxidation but which do not produce oxygen from their oxidized forms include $[MTSPP]^{4-}$, M = Zn*, Pd or $SnCl_2$ and $[MTMPyP]^{4+}$, M = Pd or $SnCl_2$.

In view of the presence and undoubted significance of manganese in photosynthetic pigments it might be expected that manganese porphyrins and related complexes should be capable of taking part in oxygen producing systems. This is particularly the case since zinc porphyrins may be active (see above) and yet replacement of manganese by zinc in, for example, thylkaloid membranes causes a decrease in the activity towards oxygen production.[308]

A number of studies of phthalocyanine and porphyrin complexes of manganese have been carried out and it is clear that both Mn^{III} and Mn^{IV} complexes can be photoreduced in the presence of water or OH^- and in the *absence* of an electron acceptor.[309-313] These complexes can be produced from Mn^{II} or Mn^{III} complexes in the presence of an electron acceptor *e.g.* quinones,[314] and the reaction can be sensitized by, for example, zinc porphyrins in suitable model membrane environments.[310]

However, all the available evidence suggests that these photoreduction reactions do not lead to oxygen formation[310-312] (although small amounts of H_2O_2 may be produced),[309,313] but rather hydroxyl radicals, which subsequently attack the somewhat sensitive skeletons of the porphyrin or phthalocyanine rings.[311,312]

Similar results have been obtained from porphyrin complexes of other metals.[315] Few attempts appear to have been made to catalyze O_2 production from these higher oxidation state manganese derivatives and this would appear to be an area warranting further study.

The supported RuO_2 catalysts described in this section, and which are superior[299] to colloidal or powdered RuO_2,[280] are probably amongst the most active for water oxidation although they suffer from the serious disadvantages that TiO_2 is an oxygen sponge and adsorbs O_2 very strongly until it is saturated, whereupon further OH^- reduction does not occur. This effect is enhanced by deposited redox catalysts and UV irradiation and varies depending upon the type of TiO_2 employed.[300,301] Oxygen absorption can be reduced by carrying out reactions in the presence of, for example, nitrate ion, but even then 20% of the O_2 formed remains adsorbed.[300]

RuO_2 supported on solids other than TiO_2, such as zeolites[268,316] and clay minerals,[317] can also be effective in the production of oxygen from water. Once again, $[Ru(bipy)_3]^{3+}$ generated thermally or photochemically using $[Co(NH_3)_5Cl]^{2+}$ as electron acceptor produces up to 95% of the stoichiometric amount of O_2 at pH 9 and this only drops to 75% at pH 1. For $[Fe(bipy)_3]^{3+}$ or $[Os(bipy)_3]^{3+}$, the pH sensitivity is more dramatic but *ca.* 100% of O_2 can be generated at pH 7 and 12 respectively using zeolite supported RuO_2 and the rate of reaction is much higher than is observed with unsupported RuO_2.[268,316]

With clay minerals, the three dimensional structure of the mineral plays an important part in determining the success of the experiment. Thus, for the normally structured hectorite, no oxygen is evolved[317] on photolysis of supported RuO_2 and $[Ru(bipy)_3]^{2+}$ in the presence of aqueous $[Co(NH_3)_5Cl]^{2+}$. This is because the cationic sensitizer is strongly adsorbed within the interlayer spaces whilst the RuO_2 aggregates on the outer surface of the mineral. Thus, RuO_2 and $[Ru(bipy)_3]^{3+}$ cannot come into mutual contact. However, if the clay is collapsed by pretreatment in air or hydrogen at 600 °C, both $[Ru(bipy)_3]^{2+}$ and RuO_2 must be on the exterior surface of the clay and O_2 evolution does occur[317] when this system is irradiated with aqueous $[Co(NH_3)_5Cl]^{2+}$.

Sepiolite has smaller interfibre distances and so penetration by $[Ru(bipy)_3]^{2+}$ does not occur and oxygen is readily evolved using this support.[317]

Finally, RuO_2 supported on WO_3 has proved more effective[49] for photochemical O_2 production from Fe^{3+} than WO_3 alone.[49] The reaction requires UV light and is inhibited by Fe^{2+} and by higher concentrations of Fe^{3+}. Quantum efficiencies are low and other metals, *e.g.* Pt, Rh or Ru on WO_3, reduce the rate of O_2 production.

61.5.4.6 Cyclic Water Cleavage — Hydrogen and Oxygen Production *via* Electron Transfer Catalysis

Examination of the various half reactions for hydrogen and oxygen production described in Sections 61.5.4.2-61.5.4.5 suggests that some of these might be coupled to give cyclic water cleavage.

For example, hydrogen can be produced from a sacrificial electron donor, a chromophore, an electron transfer catalyst and a redox catalyst. The role of the sacrificial electron donor is to

* More recent studies suggest that oxygen can be produced from $[S_2O_8]^{2-}$ and $[ZnTSPP]^{4-}$.[307]

remove the oxidized chromophore formed during the first electron transfer event and intercept the energy wasting back electron transfer reaction. Since the oxidized form of the chromophore, *e.g.* $[Ru(bipy)_3]^{3+}$ or $[ZnTMPyP]^{5+}$, can, in the presence of suitable catalysts, oxidize water, hydrogen and oxygen production should be possible. The only criteria for successful water cleavage are that the rate of oxidation of water by the oxidized sensitizer (*e.g.* equation 105) must be sufficient to compete with back electron transfer (equation 104) and that the pH values at which the two half reactions occur must be compatible.

The first reports of successful water cleavage followed the development of RuO_2 as a catalyst for O_2 production from $[Ru(bipy)_3]^{3+}$. Simply mixing colloidal RuO_2 and colloidal platinum protected by styrene–maleic anhydride copolymer with $[Ru(bipy)_3]^{2+}$ and MV^{2+} leads[318] to H_2 and O_2 production on photolysis according to equations (102)–(106) with quantum yields of *ca.* 1.5×10^{-3}. This value is 100 times smaller than that for hydrogen production in a similar system using EDTA as a sacrificial electron donor,[225] partly because back electron transfer from MV^+ to $[Ru(bipy)_3]^{3+}$ occurs at a rate comparable to that of O_2 production from $[Ru(bipy)_3]^{3+}$ and water, and partly because oxygen produced during the reaction reacts with MV^+ regenerating MV^{2+} and giving H_2O_2 but preventing H_2 production. This reaction has proved somewhat fickle and is highly dependent upon the quality of the RuO_2 catalyst. Indeed, it has recently been claimed[319] that this reaction does *not* produce H_2 and O_2.‡ Similar processes have been reported using $[ZnTMPyP]^{4+}$ as sensitizer.[94]

$$[Ru(bipy)_3]^{2+} \xrightarrow{h\nu} [Ru(bipy)_3]^{2+*} \tag{102}$$

$$[Ru(bipy)_3]^{2+*} + MV^{2+} \rightarrow [Ru(bipy)_3]^{3+} + MV^{+} \tag{103}$$

$$[Ru(bipy)_3]^{3+} + MV^{+} \rightarrow [Ru(bipy)_3]^{2+} + MV^{2+} \tag{104}$$

$$[Ru(bipy)_3]^{3+} + OH^- \xrightarrow{RuO_2} [Ru(bipy)_3]^{2+} + 0.25O_2 + 0.5H_2O \tag{105}$$

$$MV^{+} + H^{+} \xrightarrow{Pt} MV^{2+} + 0.5H_2 \tag{106}$$

In principle, since RuO_2 supported on TiO_2 is more active for O_2 production than RuO_2 alone, this catalyst, too, should be capable of interacting with $[Ru(bipy)_3]^{3+}$ at a rate competitive with that of back electron transfer. Such reactions leading to cyclic water cleavage with efficiencies up to 33% those of systems involving sacrificial electron donors and hydrogen production rates of up to 45 $cm^3\,dm^{-3}\,h^{-1}$, have been reported.[321] The amount of oxygen produced is less than stoichiometric, probably because of absorption onto TiO_2, which is known to be an oxygen sponge.[300,301] However, the rate of H_2 production is undiminished after 48 hours photolysis.

Originally, it was thought that TiO_2 was simply an innocent support for RuO_2 and Pt but subsequent study has shown that this is not the case and that cyclic water cleavage occurs, albeit with *ca.* 25% efficiency, if MV^{2+} is omitted from the mixture.[297] A diagrammatic representation of what is believed to occur in the absence of MV^{2+} is shown in Figure 11. As in other systems, light absorption forms $[Ru(bipy)_3]^{2+*}$ which injects an electron into the conduction band of TiO_2.

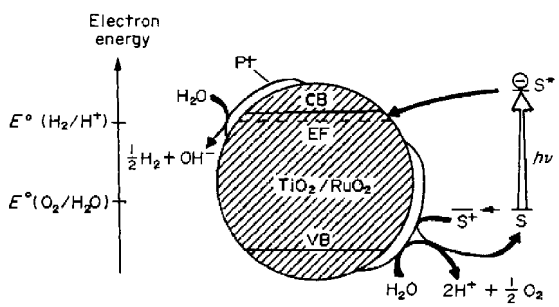


Figure 11. Schematic representation of processes involved in the photochemical decomposition of water catalyzed by $[Ru(bipy)_3]^{2+}$ (S) and colloidal TiO_2 bearing Pt and RuO_2

Charge separation occurs immediately and the electron passes to an island of platinum on the surface of the particle, where it effects proton reduction. Meanwhile, $[Ru(bipy)_3]^{3+}$ efficiently oxidizes OH^- to O_2 at the adsorbed islands of RuO_2. Thorough studies of this reaction have shown quantum yields up to 0.002 at pH 4 and hydrogen evolution rates of 0.38 $cm^3\,h^{-1}$, whereas with MV^{2+} present $\phi = 0.06$ at pH 5.5 and hydrogen is produced at 1.2 $cm^3\,h^{-1}$ from 25 cm^3 of

‡It has been suggested that H_2 production in this system may arise from the Pt support acting as an electron donor.[320]

solution. All attempts to reproduce these experiments in other laboratories have failed and it is reported that even the original investigators have been unable to repeat these observations.[322]

In the absence of a photosensitizer, $TiO_2/Pt/RuO_2$ is reported to produce H_2 and O_2 on UV photolysis in water, by direct band gap excitation, with a quantum yield of 0.3.[297]

Another system for which both H_2 and O_2 production has been observed[323] involves the use of RuO_2 and $[Ru(bipy)_3]^{2+}$ cosupported on sepiolite combined with platinum deposited on Eu^{3+} embedded in alumina. The two solids, alumina and the clay, associate in solution to give a system as shown in Figure 12. Photolysis of this system produces hydrogen and oxygen in an oscillatory reaction as shown in equations (102)–(106) but with Eu^{3+} replacing MV^{2+},[323] $[Ru(bipy)_3]^{2+*}$ reduces Eu^{3+} for H_2 production whilst $[Ru(bipy)_3]^{3+}$ oxidizes OH^- in the presence of RuO_2. Turnover numbers in this system are low, perhaps because of poisoning of the RuO_2 catalyst.

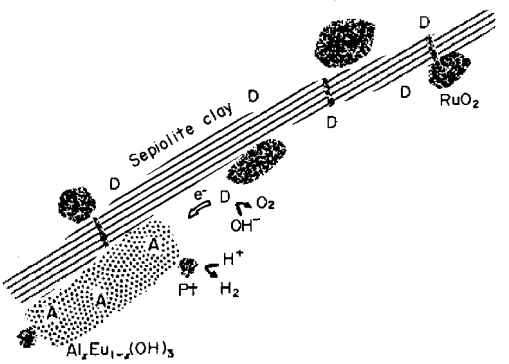


Figure 12. Schematic representation of water decomposition using sepiolite and europium(III) (A) exchanged alumina as support for $[Ru(bipy)_3]^{2+}$ (D) (reproduced from ref. 323)

Finally, it has recently been reported[320,324] that irradiation of a solution of $[Ru(bipy)_3]^{2+}$ containing colloidal $K[Fe(FeCN)_6]$ (Prussian blue, PB) produces hydrogen and oxygen continuously. It is necessary for both PB ($\lambda_{max} = 700$ nm) and $[Ru(bipy)_3]^{2+}$ ($\lambda_{max} = 452$) to be irradiated and for potassium or rubidium ions to be present in the solution (the reaction is inhibited by Na^+, Li^+ or Ca^{2+}). Evidently, PB performs a variety of different functions in this reaction. Control experiments show that it can act as an electron transfer catalyst from $[Ru(bipy)_3]^{2+*}$, as a chromophore for H_2 production from strong electron donors, and as a catalyst for O_2 production from $[Ru(bipy)_3]^{3+}$ at pH as low as 2. Quantum yields in this system are $\sim 0.1 \times 10^{-3}$ but it does appear to be a genuine example of simultaneous H_2 and O_2 production.

It must be concluded that, although intermolecular electron transfer reactions can show very high quantum yields (up to *ca.* 0.6) for both hydrogen and oxygen formation, attempts to couple production of the two gases together have been disappointing. No generally reproducible system with anything approaching commercially viable efficiency has been reported. Undoubtedly there is promise in these systems but other systems in which reversible electron donors or acceptors are employed, but for which back electron transfer is severely inhibited, must be urgently sought. This will undoubtedly require much more active redox catalysts, in particular for oxygen evolution since platinum catalysts of very high efficiency for hydrogen production are known. However, the major contribution in this field is likely to come from the use of organized assemblies (micelles, bilayers, membranes, microemulsions, *etc.*) to promote charge separation and to allow the use of reversible electron donors and acceptors with back electron transfer reactions being slowed down by intervention of the submicroscopic two phase systems.

61.5.4.7 The Use of Molecular Assemblies in Water Splitting and Related Reactions

61.5.4.7.1 Introduction

The high surface potentials and differential polarities of molecular assemblies such as micelles, vesicles and microemulsions suggest that they may be of use in effecting charge separation after a photochemical redox event either by preferential electrostatic repulsion of one of the products or by differential solubilities of the two products in the different phases. This area of research has been extensively reviewed[325–330] and we give a brief overview of the use of these systems.

61.5.4.7.2 Micelles

Molecules which have hydrophilic head groups attached to hydrocarbon chains are surface active but form micelles in water above a certain concentration (the critical micelle concentration, CMC). These micelles are generally spherical or cylindrical and have a positive, neutral or negative surface with a hydrocarbon like interior.

Although a large number of different possible ways of using micelles to promote electron transfer reactions has been discussed,[329] we consider only those in which hydrogen, or a hydrogen precursor, is generated using a metal complex as sensitizer.

The simplest use of micelles is in the solubilization of hydrophobic species and early experiments showed that [ZnTPP] in TritonX-100 micelles could act as a chromophore in the photochemical reduction of MV^{2+} by ethanethiol or TEOA. Hydrogen was produced if hydrogenase or colloidal Pt were added.[331] Zinc porphyrins in neutral micelles (TritonX-100) produce[332] hydrogen on photolysis in the presence of TEOA, bipy and $K_2[PtCl_6]$.

Secondly, micelles can be used to retard back electron transfer reactions between products produced in the primary photochemical redox reaction. Perhaps the most impressive reaction of this kind is the 1000 fold reduction in the rate of back electron transfer between methyltetradecyl-viologen cation radical ($C_{14}MV^{+}$) and $[Ru(bipy)_3]^{3+}$ formed on photolysis of $C_{14}MV^{2+}$ and $[Ru(bipy)_3]^{2+}$ in the presence of CTAC micelles rather than in free solution.[139] At the optimum $C_{14}MV^{2+}$ concentration, it is present in the free solution, does not incorporate into the micelles and does not self micellize. However, on electron transfer, the cation radical becomes amphiphilic and immediately incorporates into the micelle whilst $[Ru(bipy)_3]^{3+}$ is repelled by the positive surface of the micelle. The rate of geminate recombination (equation 104) is $<2\times10^{7}$ mol^{-1} dm^3 s^{-1}. Evidently C_{14} is the optimum chainlength, the C_{12} derivative being hydrophilic before and after electron transfer and the C_{16} and C_{18} derivatives being incorporated into the micelles as dications.[139] Similar effects are observed using $[ZnTMPyP]^{4+}$ as sensitizer, or in the absence of CTAC provided the concentration of $C_{14}MV^{2+}$ is above its CMC. Under these conditions, the molecules in free solution are reduced and then incorporated into the micelles.[139]

Replacing CTAC micelles with a cationic polysoap protecting colloidal Pt also leads to successful charge separation and in this case H_2 production is observed in the absence of a sacrificial electron donor.[138] The use of a positively charged polysoap is highly important since it allows reaction of $C_{14}MV^{+}$ with the Pt catalyst but protects $[Ru(bipy)_3]^{3+}$ from the reduced Pt particle by electrostatic repulsion.[138] It has been claimed that, in the presence of RuO_2, H_2 and O_2 are produced but details have not been published.[138]

A related example, which simply utilizes the surface potential for charge separation, involves quenching of $[Ru(bipy)_3]^{2+*}$ by PSV (see Section 61.5.4.2.3). Positively charged micelles or bilayers enhance the quantum yield for PSV^{-} formation over that in free solution by retaining it in the near surface layers of the micelle whilst expelling the positively charged $[Ru(bipy)_3]^{3+}$.[328]

The importance of surface charge is amply demonstrated by the reductive quenching of surfactant $[Ru(bipy)_3]^{2+*}$ derivatives by pyrene-*N*,*N*′-dimethylaniline (DMA). Figure 13 shows the decay of photogenerated $[Ru(bipy)_3]^{+}$ in the millisecond time domain for various different micellar environments and for free MeCN solution. Apparently the crucial step is the repulsion of DMA^{+} by the micelle and hence CTAC provides considerably more efficient charge separation than does SDS.[328]

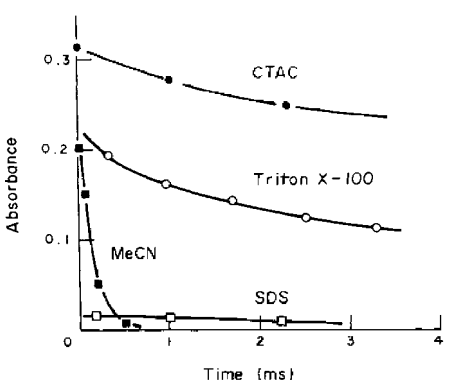


Figure 13. Decay curves of surfactant $[Ru(bipy)_3]^{+}$ (515 nm), formed from photolysis of surfactant $[Ru(bipy)_3]^{2+}$ and pyrene-*N*,*N*′-dimethylaniline, in various different environments (reproduced from ref. 328)

Very high quenching rate constants are obtained if the nitrogen derivative is attached directly to $[Ru(bipy)_3]^{2+}$ making it amphiphilic, however, very low yields of redox products are achieved even in the presence of EDTA, since back electron transfer is also extremely efficient.[149] Addition of CTAC above the CMC makes little difference but if didodecylviologen is also added, the rate of cation radical formation increases five-fold. Still higher rates of cation radical production (55×) are observed if a polysoap with pendant viologen units is added.[149]

Attachment of the ruthenium complex to the polysoap leads to even greater rate enhancements and it is believed that sequential passage of the electron from the ruthenium attached viologen after the photochemical electron transfer to neighbouring viologen units and then on down the chain of local viologens leads to efficient charge separation.[149]

Cooperative effects have been observed when surface active zinc porphyrin derivatives and amphiphilic naphthoxyviologens are irradiated in the presence of EDTA.[333] Evidence for this comes from the observation that quantum yields of radical cations of the viologens on irradiation into both the absorption band of the zinc porphyrin derivatives and of the viologen are higher than the sum of the quantum yields obtained on irradiation of the individual absorption maxima. Similar results probably occur with surface active $[Ru(bipy)_3]^{2+}$ replacing the zinc porphyrin, but selective excitation is not possible in this case.[333]

Finally, it is possible to incorporate platinum particles into micelles of $[ZnTOPyP]^{4+}$, which has a structure similar to that of $[ZnTMPyP]^{4+}$, except that one of the pyridyl nitrogen atoms is quaternized with a $C_{18}H_{37}$ chain, making it amphiphilic, either alone or diluted with CTAC.[117] Irradiation in the presence of EDTA produces hydrogen ($\phi = 0.004 \pm 0.002$) by reductive quenching of the zinc porphyrin by EDTA. Addition of MV^{2+} increases the quantum yield to 0.01, either because of reduction of MV^{2+} by $[ZnTOPyP]^{4+*}$ or because it is reduced by $[ZnTOPyP]^{3+}$ formed by the reductive quenching by EDTA.

61.5.4.7.3 Reverse micelles and microemulsions

When surfactant molecules are dissolved in organic solvents, the head groups cluster together and the hydrocarbon chains point into the bulk phase, forming reverse micelles. If water is trapped in the area of the head groups, the system is termed a microemulsion. Sometimes, a short chain alcohol (*e.g.* hexanol) is added to aid dispersion.

These systems have been used in attempts to allow charge separation in electron transfer events. For example, with microemulsions of toluene containing dodecylammonium propanoate with EDTA and $[Ru(bipy)_3]^{2+}$ in the trapped water pools, it is possible to observe reduction of bis(hexadecyl)viologen ($(C_{16})_2V^{2+}$) in the near surface region ($\phi = 0.013$). Interestingly, neither MV^{2+} nor diheptylviologen are reduced in a similar system made up of dodecane, CTAB and hexanol.[334]

It is also possible to show[98] complete charge transfer across the oil–water interface, made up of dodecylammonium propanoate, to benzylnicotinamide in the surface region. This renders benzylnicotinamide neutral and it then extracts into the toluene phase as shown by further electron transfer to 4-dimethylazobenzene (see Figure 14). Again quantum yields are *ca.* 0.013.[98]

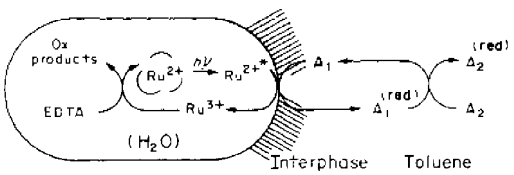


Figure 14. The separation of reduced acceptor (A_2 = 4-methylazobenzene) from oxidized donor ($[Ru(bipy)_3]^{2+}$) by an acceptor (A = benzylnicotinamide) located at the interface (reproduced from ref. 98)

The only apparent example of hydrogen production in such a system involves electron transfer from benzenethiol in $CHCl_3$/octane to water pools containing MV^{2+} and hydrogenase. The chromophore is an amphiphilic $[Ru(bipy)_3]^{2+}$ derivative embedded in the CTAC interface region.[245] The amphiphilic chromophore allows electron transfer ($\phi = 0.13$) *ca.* three times more efficiently than water soluble chromophores[245,335] such as $[Ru(bipy)_3]^{2+}$ and about five times more efficiently than when the sensitizer (*e.g.* [ZnTPP]) is present in the organic phase.

61.5.4.7.4 Vesicles

In addition to the properties of micelles described above, vesicles, which are bilayer structures and can be considered to be model membranes, separate two distinct aqueous phases: an entrapped or inner water pool and the bulk aqueous phase. In principle, therefore, electron transfer may be possible across the bilayer and the sites of hydrogen and oxygen production in a water splitting system can be separated spatially.

Although complete water splitting has not been observed in such a system, the principle can be tested since it is possible to form the vesicles in a solution containing one or more of the redox active components of an electron transfer system and then remove these components from the bulk solution, but not from the inner pools, by gel filtration or ion exchange. Other components of the electron transfer systems can then be added to the bulk water phase.

It has been reported[336] that in systems of the kind shown in Figure 15, with a sensitizer and an electron donor in the bulk phase separated from methylviologen in the inner aqueous pools, electron transfer can occur directly across the membrane. Further studies, however, showed that MV^{2+} was escaping photochemically (perhaps because of localized heating) to the bulk phase where it was reduced.[337]

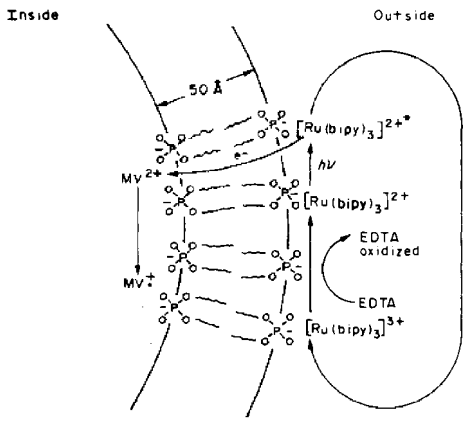


Figure 15. Originally proposed model for transmembrane electron phototransfer from EDTA to MV^{2+} *via* $[Ru(bipy)_3]^{2+}$. It was subsequently shown that MV^{2+} was escaping photochemically into the bulk aqueous phase[337] (adapted from ref. 341)

It is, therefore, necesssary to have at least one component embedded in the vesicle bilayer. In general, this has been the chromophore, which can be hydrophobic, such as tetraphenylporphyrinatozinc(II), or amphiphilic so that it aligns in the bilayer structure with the water soluble metal containing head group in the water.

For example, in the system shown in Figure 16 with EDTA or NADH as electron donor trapped in the inner pools, [ZnTPP] in the bilayer and MV^{2+} in the bulk solution, quantum yields for MV^+ formation of up to 0.1% have been observed on illumination.[186,187] This is enhanced to 0.57% if $[Ru(bipy)_3]^{2+}$ is also included in the inner pools and hydrogen is generated if either hydrogenase or polymer supported rhodium metal is added to the bulk phase. At pH 9, with $CoCl_2$, a known oxygen producing catalyst, replacing EDTA, MV^+ can still be generated photochemically. It has been suggested that this system (similar to Figure 16) provides the basis for cyclic water cleavage, but oxygen has not been detected as a product.[186,187]

Using surfactant chromophores, trans-bilayer electron transfer can also be observed, although in the absence of a mediator, the chromophore must be embedded in both surfaces of the bilayer structure. Thus, MV^{2+} in the bulk aqueous phase can be reduced by EDTA or sodium ascorbate in the inner water pools if they are separated by a bilayer consisting of 5,10,15-tris(1-methylpyridine)-4-yl-20-(4-stearoxyphenyl)porphinatozinc colyophilized with dipalmitoyl-L-phosphatidylcholine (DPPC).[338] Similar results are obtained using surfactant derivatives of $[Ru(bipy)_3]^{2+}$ and increased rates of MV^+ formation are observed if mediators such as hexadecylviologen,[98] 2-methyl-1,4-naphthoquinone (vitamin K_3)[338,339] didodecyl- or dibutyl-alloxazine (DBS)[328] are employed. The rate of electron transfer and its dependence upon chromophore concentration suggest that the electron tunnels from a chromophore on the inner surface of the vesicle to one on the outer surface rather than being carried by flipping of the surfactant chromophore from one surface to the other.[98] In the system involving amphiphilic zinc porphyrin

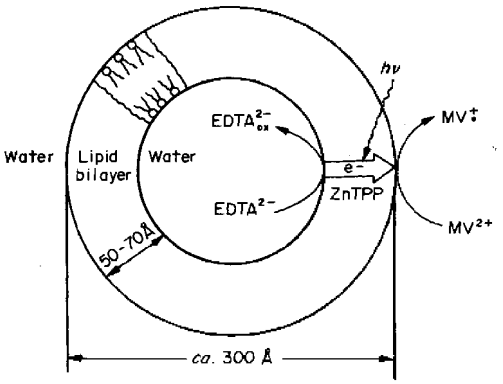


Figure 16. Scheme for successful electron phototransfer from EDTA to MV^{2+} through the bilayer of lipid vesicles containing (ZnTPP) (reproduced from ref. 186)

mediated by DBA, where the electron acceptor is disodium 9,10-anthraquinone-2,5-sulfonate (replacing MV^{2+}), there is evidence that two photons may be involved in transport of the electron across the vesicle wall (Figure 17). Unfortunately, the actual rates of geminate recombination of the oxidized form of the sensitizer and, for example, MV^{+} appear often to be higher in vesicles than in free solution, perhaps because of their higher viscosities and, although quenching rate constants can be very high, this is generally not reflected in the quantum yield for formation of MV^{+}.[328]

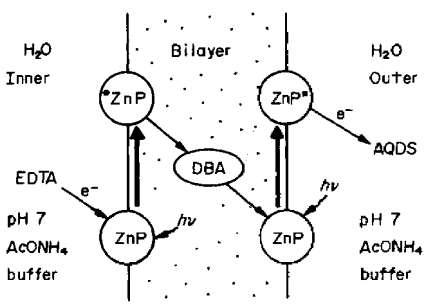


Figure 17. Schematic representation for two-step activation of electron transport across a vesicle wall. ZnP is octadecylpyridiniumyltris(4-pyridyl)porphyrinatozinc(II) cation. DBA is 1,3-dibutylalloxazine, AQDS is 9,10-anthroquinone-2,6-disulfonate (reproduced from ref. 328)

An interesting variation of this system involves embedding surface active zinc and manganese(III) porphyrins in lecithin membranes. Provided that the porphyrin is negatively charged, and with zwitterionic PSV in the bulk aqueous phase, the Mn^{III} can be photochemically oxidized to Mn^{IV}. No electron transfer from PSV^{-} to Mn^{IV} occurs, perhaps because the Mn^{IV} is deeply embedded in the membrane.[310]

Using vesicles where the amphiphilic chromophore is embedded only in the outer wall, electron transfer across the bilayer is not observed in the absence of mediators whether the EDTA is in the inner pools with MV^{2+} in the bulk phase or *vice versa*.[338,339] With EDTA in the inner pools, electron transfer can, however, be effected on addition of, for example, ubiquinone, ZnTPP or H_2TPP to the bilayer. In the last two cases, electron transfer is much more efficient than when the amphiphilic zinc porphyrin is omitted.[339]

Finally, a number of studies have employed viologens in the bilayer, either added as an amphiphilic reagent to DPPC,[340] or as the sole component of the vesicle walls.[337,341,342] In the latter cases, double bonds in the hydrocarbon chain of the viologen have been polymerized to give added stability and rigidity to the bilayer structure.

For added viologens, photochemical electron transfer from inner pools containing EDTA or $K_2C_2O_4$ and $[Ru(bipy)_3]^{2+}$ or $[ZnTMPyP]^{4+}$ to methylene blue, $[Fe(CN)_6]^{3-}$, $[\{Ru(bipy)_2(H_2O)\}_2O]^{4+}$ or $[SiMo_{12}O_{42}]^{8-}$ was observed and in the absence of an electron acceptor in the bulk, viologen cation radical was formed. Again, tunnelling of an electron from a reduced viologen on the inner surface to one on the other surface is believed to occur. Quantum yields up to 0.1 have been observed.[340]

Using the polymerized viologen bilayers, the viologen units were removed from the outer surface to which they were attached by ester linkages by reaction with iminoethanol. Photolysis with $[Ru(bipy)_3]^{2+}$ in the bulk phase then led to viologen cation radical formation on the inner surface. Presumably the iminoethanol groups acted as electron donors.[342]

Finally, vesicles have been used to store reducing equivalents by incorporating $C_{14}MV^{+}$, formed from $C_{14}MV^{2+}$ on irradiation in the presence of EDTA and $[Ru(bipy)_3]^{2+}$, as multimers (monomers are obtained in the presence of CTAC micelles). These multimers are more stable to air than the monomers but generate hydrogen from water on the addition of carbowax protected colloidal platinum.[343]

From the foregoing discussion, it would appear that ordered assemblies have enormous potential for increasing the efficiency of water splitting systems since they can, under favourable circumstances, lead to efficient charge separation, although considerably more research in this area is required. In particular, the development of more efficient neutral electron transfer catalysts will assist electron transfer across bilayers. Bis(2,3′-diphenylditholato)nickel has been successfully employed[344] as such a neutral electron transfer catalyst by dissolving it in diphenyl ether containing dicyclohexano-18-crown-6 supported in a millipore filter. Electron transfer occurs from EDTA *via* $[Ru(bipy)_3]^{2+}$ and MV^{2+} on one side of the membrane to $[Fe(CN)_6]^{3-}$ on the opposite side. Direct transfer from $[Ru(bipy)_3]^{2+*}$ *via* the nickel complex is also possible if SDS is added to the aqueous solution containing $[Ru(bipy)_3]^{2+}$. The more efficient electron transfer quenching by nickel in this case is believed to arise because the SDS molecules take $[Ru(bipy)_3]^{2+}$ to the H_2O/Ph_2O interface. The electron is carried across the membrane by the $[Ni(S_2C_2Ph_2)_2]^{0/-}$ couple.[344] Other neutral electron transfer catalysts include zwitterionic sulfonated viologens (see Section 61.5.4.2.3).

The development of highly selective redox catalysts for H_2 production (see above) and investigations of oxygen producing reactions are also goals worthy of the highest priority. Other types of ordered assembly that would appear worthy of study in water-splitting systems include polyelectrolytes, particularly since their charged surfaces can enhance certain quenching rate constants by up to three orders of magnitude,[345] and solid supports bearing a surface charge.

Some work on solid supports has been described in Section 61.5.4.5.3(ii), but another interesting series of reports concerns the use of colloidal SiO_2. The negatively charged surface adsorbs $[Ru(bipy)_3]^{2+}$ and evidently holds it in such a way that oxygen does not quench the emission whereas the positively charged MV^{2+} does. Very efficient formation of MV^{+} is observed in the presence of EDTA or TEOA.[346]

Furthermore, whereas back electron transfer from the radical anion derived from the zwitterionic *N,N′*-bis(3-sulfonatopropyl)-2,2′-bipyridinium ion (DQS) to $[Ru(bipy)_3]^{3+}$ in alkaline homogeneous solution is so rapid that redox products cannot be observed on flash photolysis, in the presence of SiO_2 colloids the rate constant for this reaction, k_b, is 10^7 mol^{-1} dm^3 s^{-1}.[145] The role of the SiO_2, which has a negatively charged surface at this pH, is to repel DQS^{-} whilst strongly attracting $[Ru(bipy)_3]^{3+}$. In homogeneous solution these two products attract one another on account of their opposite charges and cage escape does not compete with back electron transfer. In addition, SiO_2 prevents DQS^{-}, once it has escaped from the cage, from returning into the environment of $[Ru(bipy)_3]^{3+}$ and hence further retards the back electron transfer. In the presence of TEOA and colloidal platinum, hydrogen is evolved with $\phi = 2.2 \times 10^{-3}$ at pH 8.5.

Similar results are obtained[347,348] with PSV except that no effect on cage escape is observed, just a retardation in the subsequent back electron transfer by a factor of 100 compared with homogeneous solution. The less negative reduction potential of PSV means that hydrogen cannot be generated at the high pH required for SiO_2 to have a negatively charged surface. Anthraquinone sulfonates can, however, be reduced by PSV^{-} generated in this way.[349,350]

61.5.5 PHOTOELECTROCHEMICAL DECOMPOSITION OF WATER

Although it is apparent from the foregoing discussion that the simultaneous catalytic production of hydrogen and oxygen from water has only been demonstrated in a very few cases and even most of these have proved irreproducible, all of the systems produce hydrogen and oxygen in very close proximity to one another. A possible way to surmount this problem is to use photoelectrochemistry and generate hydrogen at one electrode and oxygen at another. These electrodes can be in the same or different compartments but if they are in different compartments, changes in pH will occur and replenishment of H^+ in the cathode compartment and of OH^- in the anode

compartment will be necessary.* Using the same compartment can lead to short circuiting of the desired reactions. A large amount of research has been carried out into the photoelectrochemical production of hydrogen and/or oxygen from $[Ru(bipy)_3]^{2+}$.

It is possible to generate hydrogen from a solution containing $[Ru(bipy)_3]^{2+}$, MV^{2+} and a sacrificial electron donor such as TEOA, EDTA or cysteine at a pH (8–10) where reduction of H^+ by MV^+ is not thermodynamically possible. This is achieved[351] by attaching the solution *via* platinum anode and cathode to water at a lower pH and joining the two solutions by an agar/KCl bridge. Hydrogen is then produced from the cathode in the solution which does not contain photosensitizer *etc.* At lower pH values in the anode compartment, some hydrogen may be produced by direct Pt catalyzed reduction of protons by MV^+. This problem can be overcome by use of a mercury anode[352] at which the overpotential for H_2 formation is higher and then both cathode and anode compartment can contain solutions at pH 4.7 with EDTA as the irreversible electron donor.[352]

Alternatively, hydrogen can be generated at a remote cathode from $[Ru(bipy)_3]^+$ generated by reductive quenching of $[Ru(bipy)_3]^{2+}$ by Et_3N.[353]

More effort has been devoted to studies of O_2 production. In this case, the cathode compartment contains $[Ru(bipy)_3]^{2+}$ and an electron acceptor such as $[S_2O_8]^{2-}$,[354–356] $[Co(C_2O_4)_3]^{3-}$,[351] $[Co(NH_3)_5Cl]^{2+}$,[353,357] or Tl^{3+},[353] and a platinum or carbon cathode. The pH of the anode compartment depends not only on the oxidation potential of the $[Ru(bipy)_3]^{3+}$, which can be varied by use of substituted bipyridyls, but also on the overpotential of the anode material for O_2 production.

For example, systems based on $[Ru(bipy)_3]^{2+}$ itself can produce oxygen at pH > 7 at a Pt anode,[351] whereas smooth oxygen production is observed at pH 4.7 from an anode prepared from RuO_2 deposited on titanium sheet.[354,358] Still lower pH values for the anode compartment are possible if $[Ru(bipy)_2L]^{2+}$ (L = dipropyl 2,2′-bipyridyl-4,4′-dicarboxylate) for which $E°(3+/2+)$ is 1.59 V (*vs.* SCE).[356] There is, however, a suggestion that using RuO_2 and $[Ru(bipy)_3]^{2+}$, O_2 production can occur from an anode at pH as low as 1.0.[358]

In the case of the substituted bipyridyl[356] it is found that the rate of O_2 production is dramatically enhanced by addition of Ce^{3+} to the cathode compartment. Apparently, $[Ru(bipy)_2L]^{3+}$ decomposes rapidly once formed so that not all of it arrives at the cathode. Ce^{3+} reduces $[Ru(bipy)_2L]^{3+}$ in bulk solution and Ce^{4+} accepts the electron from the cathode.

The chemistry of these systems is identical to that already described for O_2 and H_2 production in homogeneous systems except that MV^+ or $[Ru(bipy)_3]^{3+}$ generated during the photochemistry of the bulk solution then regenerate MV^{2+} or $[Ru(bipy)_3]^{2+}$ by donation or acceptance of an electron at the electrode. Photopotentials of ~1.0 V and currents of ~1 mA can be generated for long periods in this way. Similar photoelectrical cells using metal phthalocyanine or porphyrin sensitizers have also been developed.[359–362]

There have been two reports of cyclic water cleavage in a photoelectrochemical system. The first simply involves[358] addition of protected colloidal Pt to a solution containing MV^{2+} and $[Ru(bipy)_3]^{2+}$ in 0.1 M H_2SO_4. Instead of MV^{2+} injecting an electron into the electrode for remote H_2 production, hydrogen production is achieved by reduction of H^+ by MV^+ catalyzed by colloidal Pt. The $[Ru(bipy)_3]^{3+}$ which accumulates then receives an electron from the Pt electrode and oxygen formation occurs at an RuO_2 electrode in H_2SO_4 (0.5 mol dm^{-3}) separated from the cathode compartment by nafion. Apparently H_2 and O_2 are produced photochemically with a photocurrent of 0.2 mA. It is difficult to see how this reaction occurs with such efficiency since the rate of diffusion of $[Ru(bipy)_3]^{3+}$ to the electrode and the rate of H_2 production from MV^+ and H^+ are expected to be much slower than back electron transfer between $[Ru(bipy)_3]^{3+}$ and MV^+.[358] Chinese workers have reported that cells based on n-TiO_2/NaOH//$[Rh(bipy)_3]Cl_3$/Pt or Pt/$[Ru(bipy)_3]Cl$//$[Rh(bipy)_3]Cl_3$/Pt also produce H_2 and O_2 on photolysis.[363]

One other approach to the photoelectrolysis of water that has been adopted involves the photosensitization of semiconductor electrodes such as TiO_2,[362,364,365] $SrTiO_3$[365,366] or SnO_2[265,365,367] by, for example, $[Ru(bipy)_3]^{2+}$. The photochemically excited state of the chromophore injects an electron into the conduction bond of a semi-conductor; this is then passed *via* an external circuit to a platinum electrode for H_2 production. The oxidized form of the quencher then forms O_2 apparently in an uncatalyzed reaction.† Unfortunately, all such systems

* Using different compartments may, however, overcome reactions of oxygen with, for example, MV^+, which can drastically reduce rates of water decomposition.

† There is some evidence that photoexcited $[Ru(bipy)_3]^{3+}$ oxidizes water much more rapidly than does the ground state.[265]

that have been reported require an external bias (usually *ca.* 1.0 V) and it has been shown that O_2 adsorbed on the semiconductor leads to low rates of electron transport[364] and even adsorbing the chromophore on the electrode physically[265] or chemically[365] does not lead to substantial increases in efficiency.

The only related system which allows H_2 production with lower bias potentials is that derived from adsorption of $[Ru(bipy)_2(MeOCH_2CH_2OMe)]^{2+}$ onto a polysulfurnitride electrode. Hydrogen production is observed on irradiation of the face perpendicular to the fibre bundles with a bias of only −0.1 V relative to SCE.[368]

Finally, polymolybdate[369,370] and tungstate[371] ions can be used for photogalvanic hydrogen production on irradiation with UV light. The absorption of light produces OH· identified by spin trapping and a hydroxomolybdenum(V) species, which injects an electron into a platinum electrode. Hydrogen is produced at a remote platinum cathode in H_2SO_4 (2.5 mol dm^{-3}). Unfortunately, oxygen does not appear to be produced from OH· but rather oxidation of the molybdate occurs to give peroxomolybdate species.[370] Using tetrathiomolybdate and a carbon anode,[372,373] hydrogen can again be produced photoelectrochemically and the hydrolyzed catalyst can be recycled by addition of H_2S. The overall reaction is then the photochemical production of hydrogen and sulfur from H_2S.[373]

61.5.6 COORDINATION COMPLEXES AS CATALYSTS FOR THE ELECTROCHEMICAL PRODUCTION OF HYDROGEN OR OXYGEN FROM WATER

61.5.6.1 Hydrogen Production

In view of its high overpotential for the production of hydrogen from water, the mercury electrode allows electrochemical evaluation of possible catalysts for proton reduction since redox potentials and efficiencies for hydrogen production can be measured. In general, a species that is catalytically active for hydrogen production will give an amplified wave in both polarography and cyclic voltammetry.

The first waves of this kind were observed by Brdicka[374] in solutions containing proteins and Co^{2+} at *ca.* −1.3 V (*vs.* SCE). Subsequently, numerous studies have shown that these waves are produced from solutions of Co^{2+} or Co^{3+} containing a wide range of sulfur containing compounds.[375,376] Cysteine complexes have especially been studied. It seems that complex formation is very important[377–383] and at least two functional groups on the ligand must coordinate[378] to the metal atom. One of these must be sulfur, whilst the other can be $-CO_2H$, $-NH_2$, *etc.*[378] Analogous complexes with oxygen replacing sulfur do not produce the effect.[382] Nitrohydroxylaminate[384–386] anion or NCS^-[387,388] will also produce a catalytic wave and some investigators have observed catalytic hydrogen waves in the absence of added ligand.[389–391] Similar complexes of Ni^{2+} also give catalytic hydrogen waves in polarography.[375]

It is known that a number of metals which do not amalgamate with mercury are capable of lowering the overpotential of hydrogen production at mercury electrodes and indeed catalytic hydrogen waves attributable to metal deposition can be observed in polarograms of simple salts of Ni,[392] Ru,[393–395] Rh,[394] Ir,[394,395] and Pt.[394,395] For Au, Ag, Cu and Pd, which amalgamate with mercury, catalytic hydrogen waves are not observed.[394]

Interestingly, a catalytic hydrogen wave is obtained from bis(dithiocarbamato)zinc(II) at a carbon (paste or graphite) electrode although not at mercury.[396] This is probably because the zero valent complex is unstable with respect to loss of zinc metal to form an amalgam, whilst it is sufficiently stable on carbon to promote catalysis.[396]

Initially, it was believed[397] that the Brdicka waves were attributable to cobalt deposition on the mercury surface leading to a lowering of hydrogen overpotential, and indeed this may be the case when no ligand is present or in the presence of, for example, histidine.[377] However, attempts[379] to measure directly the effect of cobalt deposition by coating the mercury surface with cobalt suggest that it does not lower the overpotential for hydrogen significantly and it has been suggested that even in the absence of added ligands, a zerovalent complex may be the active species in the catalytic cycle.[389]

Further evidence that cobalt metal is *not* responsible for the catalytic hydrogen waves comes from the observation that the higher the stability of the complex formed between the sulfur-containing ligand and Co^{2+}, the more pronounced is the catalytic wave.[378] This is confirmed since

the wave is depressed in acid solution[378] where certain functional groups can be protonated off the cobalt leading to a reduction in the stability of the complex.

The generally accepted,[376] although not fully proven, mechanism for the catalytic wave is as shown in equations (107)–(109) and involves reduction to a zerovalent complex which is the catalytically active species. Whether the catalysis involves two or one electron steps (Co^{2+} or Co^{+}) intermediates is not known but it is probable that the neutral zerovalent complex is adsorbed on the electrode surface.[380,396]

$$M^{II}L_2 + 2e \rightarrow M^0L_2 \quad (107)$$

$$M^0L_2 + nH^+ \rightarrow M^0L_2H_n \quad (108)$$

$$M^0L_2 + ne \rightarrow M^0L_2 + 0.5nH_2 \quad (109)$$

An alternative mechanism (equations 110–112) has been reported to operate in certain cases, for example for ML_2, $M = Co^{2+}$ or Ni^{2+}, $L = [ROCS_2]^-$, $[R_2NCS_2]^-$ or $[RHNCS_2]^-$.[376] A related mechanism is also believed[398] to be responsible for the extremely efficient (*ca.* 2×10^5 catalyst turnovers h^{-1}) catalytic reduction of water at a mercury electrode using $[MH(PEt_3)_3]^+$, $M = Pt$ or Pd. In these cases the system is further complicated since cyclic voltammagrams give inverted and amplified waves (Figure 18). In the first negative sweep, it is believed that a two-electron reduction (equation 113) occurs to give a monolayer of adsorbed $[MH(PEt_3)_3]^-$ which is not catalytically active. The reductive catalytic cycle is then initiated (equation 114) on the first subsequent positive sweeps by a one electron oxidation to $[MH(PEt_3)_3]_{ads}$·. The catalytic cycle (equations 115–117) then continues until the potential is insufficiently reducing to drive equation (115). On the second and subsequent negative scans, the catalytic cycle restarts once the potential is sufficiently reducing to drive equation (115) and continues until the potential allows reduction of $[MH(PEt_3)_3]_{ads}$· to the catalytically inactive $[MH(PEt_3)_3]_{ads}^-$ (equation 118). At concentrations higher than 5×10^{-4} mol dm^{-3} the cyclic voltammograms are complicated by desorption of $[M(PEt_3)_3]$. Interestingly, solutions containing platinum(IV) complexes and PH_3 also give catalytic hydrogen waves in their polarograms but these have been attributed to reduction of $[PH_4]^+$ catalyzed heterogeneously by the platinum complex.[399]

$$ML_n + H^+ \rightleftharpoons [ML_nH]^+ \quad (110)$$

$$[ML_nH]^+ + e \rightarrow ML_n + 0.5H_2 \quad (111)$$

$$ML_n + HA \rightleftharpoons [ML_nH]^+ + A^- \quad (112)$$

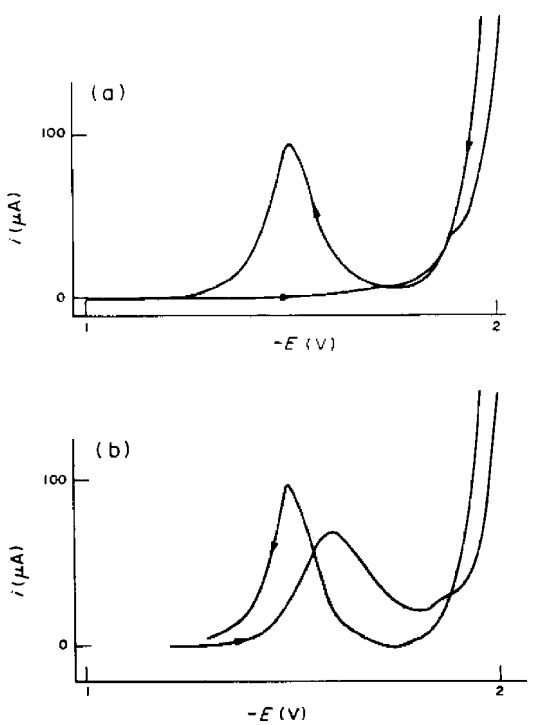


Figure 18. Cyclic voltammograms of $[PtH(PEt_3)_3]^+$ (1.5×10^{-4} mol dm^{-3}) in phosphate buffer (pH 6.88) at a mercury drop electrode: (a) first scan; (b) second and subsequent scans

$$[PtH(PEt_3)_3]^+_{aq} + 2e \rightarrow [PtH(PEt_3)_3]^-_{ads} \quad (113)$$

Initiation $$[PtH(PEt_3)_3]^-_{ads} - e \rightarrow [PtH(PEt_3)_3]^{\cdot}_{ads} \quad (114)$$

Catalytic cycle $$[PtH(PEt_3)_3]^{\cdot}_{ads} + e + H^+ \rightarrow [Pt(PEt_3)_3]_{ads} + H_2 \quad (115)$$

$$[Pt(PEt_3)_3]_{ads} + H^+ \rightarrow [PtH(PEt_3)_3]^+_{ads} \quad (116)$$

$$[PtH(PEt_3)_3]^+_{ads} + e \rightarrow [PtH(PEt_3)_3]^{\cdot}_{ads} \quad (117)$$

Termination $$[PtH(PEt_3)_3]^{\cdot}_{ads} + e \rightarrow [PtH(PEt_3)_3]^-_{ads} \quad (118)$$

61.5.6.2 Oxygen Production

There are comparatively few coordination complexes which lower the overpotential for oxygen production. Hydroxides of both iron(II)[400] and cobalt(II)[400,401] catalyze oxygen production at a rotating platinum disc electrode at high pH. The mechanism of the reaction is analogous to that proposed for the catalytic production of oxygen from, for example, $[Ru(bipy)_3]^{3+}$ (see section 61.5.4.5). Related to this is the use of $[\{(NH_3)_5Co\}_2O]^{5+}$ for the catalytic production of oxygen or hydrogen peroxide[402] at platinum[403] or mercury[402] electrodes.

Ruthenium trichloride catalyzes the production of oxygen at a platinum anode[404] *via* higher oxidation state species, whilst one of the most effective catalysts for oxygen or chlorine evolution is formed by reduction of a solution containing $[Fe_2(SO_4)_3]$ and $K_3[Ru(CN)_6]$.[404] This leads to a film on the electrode of ruthenium purple, $Fe_4[Ru(CN)_6]_3$, with a structure analogous to that of Prussian blue. Oxygen can then be produced at 0.2 V *vs.* SCE.[404]

Finally, both manganese(II) gluconate[405] and alkaline solutions of cobalt phthalocyanines[406] also promote catalytic oxygen evolution.

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62.1.1 INTRODUCTION

In this chapter it is hoped to review in general terms the major subject of metals in biology, and to draw attention to appropriate further reading for the expansion of particular topics. The essential role of metal ions in a wide range of biological processes is now well known and hardly requires elaboration! It should be noted that important advances have been made in the last two decades, and current studies are serving to demonstrate the breadth of the subject and the exciting prospect that lies ahead.

Li	Be										
Na	Mg										
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
Rb	Sr	Y	Hf	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd
Cs	Ba	La	Zr	Ta	W	Re	Os	Ir	Pt	Au	Hg

Vanadium and chromium appear to be essential elements, while this claim has also been made recently for tin (N. F. Cardarelli, 'Tin as a Vital Nutrient: Implications in Cancer Prophylaxis and other Physiological Processes', CRC Press, Fort Lauderdale, 1985). For a recent account of the biochemistry of the trace elements see 'Biochemistry of the Essential Ultratrace Elements', ed. E. Frieden, Plenum, New York, 1984

Figure 1 Metal ions of biological significance

The metal ions of major biological significance are indicated in Figure 1, which shows part of the Periodic Table. Some information on the distribution and concentration levels of these metals in living systems is shown in Table 1. The transition metals and zinc are usually regarded as trace elements, as they are present in very small amounts. Of the transition elements, iron is the most abundant metal, and probably the most well studied. Iron is essential for all living systems with the exception of certain members of the lactic acid bacteria, which grow in environments notoriously low in iron, such as milk. Lactic acid bacteria are devoid of cytochromes, peroxidases

Table 1 Metal Levels in Adult Humans

Metal	*Total (70 kg adult)* (mg)	*Whole blood* ($\mu g\ dm^{-3}$)	*Red cells* ($\mu g\ dm^{-3}$)	*Liver*[a] ($\mu g\ g^{-1}$ dry weight)	*Muscle*[a] ($\mu g\ g^{-1}$ dry weight)	*Kidneys*[a] ($\mu g\ g^{-1}$ dry weight)
Na	100	1960	280	3000	2600–8000	10 000
K	140	1700	3600	8500	16 000	8300
Mg	20	24	57	590	900	630
Ca	1000	61	3.2	100–360	140–700	400–820
V	15	<0.0002	<0.056	0.006	0.02	0.03
Cr	2	2–5	0.037	0.02–3.3	0.024–0.084	0.05–4.7
Mn	12–20	69	0.035	3.6–9.6	0.2–2.3	3.3
Fe	4000[b]	450	1050	250–1400	180	170–710
Co	1.5	<0.04	<0.086	0.06–1.1	0.028–0.65	0.035–0.31
Ni	10	2–4	0.083	0.02–1.81	1–2	0.6–1.8
Cu	50–120	1000	0.98	30	10	16
Zn	1400–3000	9000	14.2	240	240	200
Mo	9–10	0.001	0.017	1.3–5.81	0.018	0.9–3.11
Sn		0.29 (?)	0.38	0.23–2.3	0.33–2.4	0.68–4.4

[a] H. J. M. Bowen, 'Environmental Chemistry of the Elements', Academic, London, 1979.
[b] Distributed as hemoglobin (2600), ferritin (450), hemosiderin (400) non-heme enzymes (400), myoglobin (138), catalase (8), transferrin (4).

and heme enzymes of all types, and present an interesting study of the way in which nature circumvents this lack of iron. In some cases cobalt or manganese(III) is used instead.

The metals of Groups IA and IIA, sodium, potassium, magnesium and calcium, are much more important in a quantitative sense, although they have been less well investigated. These cations are, of course, less easy to study as they form complexes only weakly, and cannot be studied by simple spectroscopic techniques. However, the increasing application of NMR methods to the IA and IIA elements should advance the understanding of their biochemistry. It should be noted that these four cations are distributed selectively in biological systems. In general, K^+ and Mg^{2+} are concentrated inside cells, while Na^+ and Ca^{2+} are rejected by the cell and are extracellular cations. Calcium may also be stored in internal organelles, but cell cytoplasm will be low in calcium. This selective distribution of these cations is essential to an understanding of their biological function.

Attention should be drawn to molybdenum, which at present appears to be the only second row transition element of biological significance. It may well be that other transition metals have biological roles which are unrecognized at present. The need for metal ions is usually demonstrated initially by nutrition studies, for example by showing that the growth of an organism is dependent on the supply of a particular metal. Such conditions are often quite difficult to achieve, as sufficient metal may be supplied adventitiously as impurities in other compounds or from other sources. Thus it is only comparatively recently that the role of nickel has been fully appreciated. While its presence in the enzyme urease from jack bean has been known for decades, it was not recognized that nickel was an essential growth requirement for a number of microorganisms, due, at least in some cases, to the adventitious supply of nickel from stainless steel equipment! There is now good evidence that vanadium and chromium have biological functions, as distinct from biochemical and physiological effects, while there is currently some interest in arsenic, aluminum and tin.

Inorganic biochemists are also interested in two other classes of metals: those that occur as environmental or other pollutants (lead, cadmium, mercury, aluminum in Alzheimer's disease *etc.*), and those which are important in medicine (lithium in mental health, platinum in anticancer drugs, gold in rheumatoid arthritis). The last group is considered in Chapter 62.2.

62.1.1.1 Binding Groups for Metals in Biology

Metal ions in biology will usually be bound by much larger and more complicated ligands than the relatively simple ones usually encountered in coordination chemistry. The fact that such complicated ligands are used in biology is reflected in the remarkable and subtle ways in which these ligands control the function and reactivity of a particular metal in biology, for example iron in the heme proteins. Thus, the ligand may control the coordination number, the detailed coordination geometry, the spin state, redox potential and rate of electron transfer of a bound transition metal ion. It may provide a hydrophobic environment around the metal centre that will control various electrostatic interactions and the reactivity of the group.

Metal ions may be bound by ligands from the following major classes: proteins, *via* amino acid side chains; nucleic acids and nucleotides; various macrocyclic tetrapyrrole ligands; metals may occur as dimers or clusters having sulfido (S^{2-}) or oxo (O^{2-}) bridging ligands. In the last two classes, the coordination number of the metal may be completed by ligand groups from proteins. Discussion of macrocyclic ligands and ligands of biological importance will be found in Chapters 21 and 22 respectively of Volume 2.

Certain amino acid residues in proteins are particularly important ligands, notably cysteine and histidine which provide SH and imidazole groups respectively. These are shown in Figure 2, which also lists other important residues. The γ-carboxyglutamate residue found in the 'gla' proteins is noteworthy as an important binding group for Ca^{2+}, while other high affinity sites for calcium contain the β-hydroxyaspartate residue, one not found previously in proteins.

Several macrocyclic ligands are shown in Figure 2. The porphyrin and corrin ring systems are well known, the latter for the cobalt-containing vitamin B_{12} coenzymes. Of more recent interest are the hydroporphyrins. Siroheme (an isobacteriochlorin) is the prosthetic group of the sulfite and nitrite reductases which catalyze the six-electron reductions of sulfite and nitrite to H_2S and NH_3 respectively. The demetallated form of siroheme, sirohydrochlorin, is an intermediate in the biosynthesis of vitamin B_{12}, and so links the porphyrin and corrin macrocycles. Factor 430 is a tetrahydroporphyrin, and as its nickel complex is the prosthetic group of methyl coenzyme M reductase. F430 shows structural similarities to both siroheme and corrin.

Donor groups of protein side chains —CONHCHCONH—
|
X

Oxygen donors

Aspartic acid —CH_2CO_2H

β-Hydroxyaspartic acid —$CH(OH)CO_2H$

Glutamic acid —$CH_2CH_2CO_2H$

γ-Carboxyglutamic acid —$CH_2CH(CO_2H)_2$

Tyrosine —CH_2–C$_6$H$_4$–OH

Nitrogen donors

Histidine —CH_2–imidazole

Lysine —$CH_2CH_2CH_2CH_2NH_2$

Arginine —$CH_2CH_2CH_2NH$–C(=NH_2^+)–NH_2

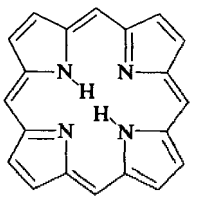
Amino terminus
Deprotonated peptide

Sulfur donors

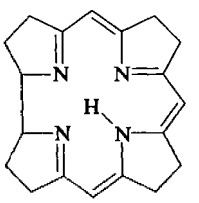
Cysteine —CH_2SH

Methionine —CH_2CH_2SMe

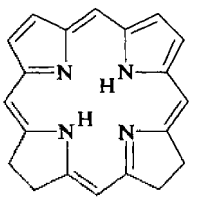
Tetrapyrrole macrocycles



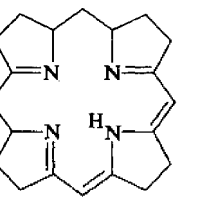
Porphyrin



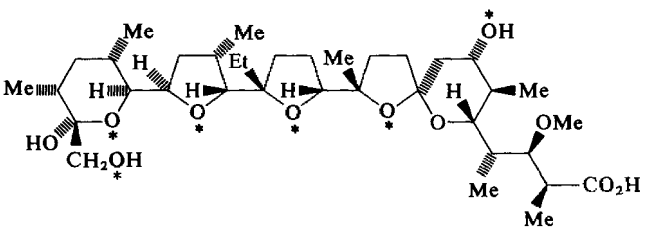
Corrin



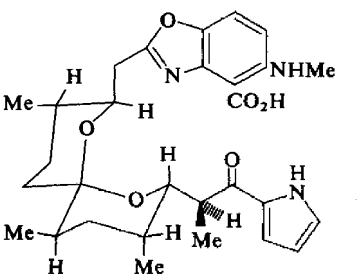
Chlorin



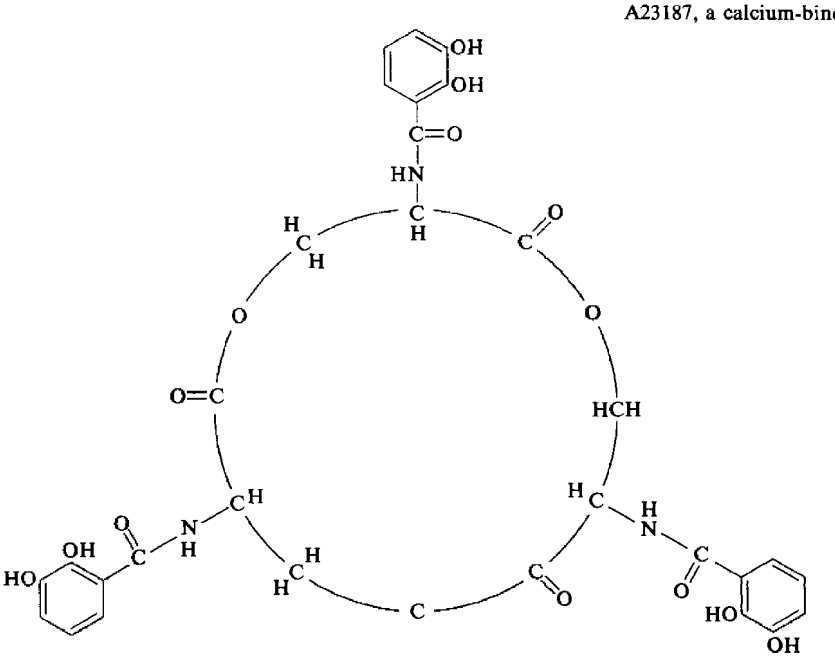
Factor 430



Monensin, a sodium-binding monocarboxylic acid ionophore



A23187, a calcium-binding ionophore



Enterochelin, an iron carrier

Figure 2 Some important biological ligands

It is of interest to compare the porphyrin and corrin macrocycles, and to consider the reactivities of porphyrin- and corrin-bound metal ions. These may be related to the size of the cavity. The corrin macrocycle provides a smaller cavity, into which cobalt fits tightly in the B_{12} coenzymes. Thus the cobalt does not move relative to the corrin plane, and remains coplanar with the four nitrogen donor atoms. The cobalt remains low-spin, and reactivity is controlled by the loss of the axial ligands, giving five- and four-coordinate species.

The cavity in the porphyrin ligand is larger. Both Fe^{II} and Fe^{III} are too small to fit tightly into the cavity, and the porphyrin ring must be buckled to allow good interaction between the metal and the donor atoms. As a result of this misfitting, the iron centre is able to move in and out of the plane, in response to various factors, with resulting changes from low-spin to high-spin from heme to heme. This will have important implications for the control of redox potential and the rates of electron transfer.

In some instances, metals are bound by small ligands of high specificity, such as the siderophores (for iron) and ionophores (for alkali and alkaline earth metals). These will be discussed fully in later sections.

It is possible on chemical grounds to predict the likely binding groups for particular metals. These binding groups may come from more than one biological molecule if the metal serves as a bridge. These conclusions are based upon a detailed consideration of formation constant data, and also upon the qualitative trends suggested by such concepts as 'hard' and 'soft' acids and bases. They are also embodied in the use of certain reagents as 'spot tests' for metals in qualitative analytical chemistry. The ligand preferences of some biologically important metals are shown in Table 2. In metal–protein complexes, the nature of the ligand groups will also be determined by the protein structure around the metal, as the binding of the first ligand group may determine which groups are then near enough to the metal to act as ligands.

Table 2 Likely Binding Groups for Biologically Important Metal Ions

Metal	*Binding group*
K^+	Singly charged or neutral oxygen ligands
Mg^{2+}	Carboxylate; phosphate; nitrogen ligands
Ca^{2+}	Carboxylate, particularly 'gla' proteins; less affinity than Mg^{2+} for nitrogen ligands; phosphate
Mn^{2+}	Similar to Mg^{2+}
Mn^{3+}	Imidazole; tyrosine; sulfur donor (in acid phosphatase)
Fe^{2+}	Porphyrin; S^{2-}; thiols; NH_2; carboxylates; O^{2-}
Fe^{3+}	Porphyrin; carboxylate; tyrosine and other phenolic groups; NH_2; S^{2-}; hydroxamic acids; O^{2-}
Co^{n+}	Corrin
Ni^{2+}	Porphyrin; (corrin?), SH?
Cu^+	SH
Cu^{2+}	Amines; carboxylates; imidazole
Zn^{2+}	Imidazole; cysteine; glutamic acid
Cd^{2+}	SH

62.1.1.2 Roles for Metals

The requirement for a particular metal ion must be related to its chemical, structural and possibly redox properties, and the ease with which these properties can be tuned finely by the biological ligand. The function of the metal ion depends upon its size and charge, and, if appropriate, upon its redox properties. The IA cations are poor polarizers and do not bind to ligands strongly. This means that they occur effectively in solution as free ions, the distribution of which is controlled by membranes. The presence of these charge and concentration gradients across membranes can be exploited in a number of control processes. The other metals, especially the transition metals, bind firmly to their ligands. They can do this selectively, and if appropriate affect the electron distribution in the ligand so as to enhance its reactivity. Alternatively, binding of a metal may result in stabilization of ligand conformations. The cations can also bind to two ligands, and so serve to bridge or crosslink groups. Finally, the nature of the ligands can control the redox potential of a transition metal couple, in direct and indirect ways, and so allow the tuning of E_0 values. This brief discussion has introduced some key words such as 'control', 'stabilization', 'selectivity', 'crosslinking', 'reactivity' and 'tuned redox potential', which indicate the potential roles for metals.

It is possible to make some immediate generalizations as to the major functions of particular groups of metals. The transition elements, which are firmly bound to their biological ligands, usually have a redox function, in which change in the oxidation state of the metal is linked either to electron transfer or to redox reactions of a substrate. Manganese, as Mn^{III}, has a redox role in certain superoxide dismutases and is present in acid phosphatase, but in general occurs in biology as Mn^{2+}, with a function similar to Mg^{2+}. Indeed, these two cations may sometimes displace each other, depending on their supply. The transition metals iron and copper are also involved in the transport and storage of dioxygen, where there is some reversible electron transfer between the transition metal and the substrate.

While nickel has a redox role, for example in hydrogenases, it may well also function as a strong Lewis acid in the enzyme urease, where the reactivity of urea towards hydrolysis is enhanced by coordination and polarization. Zinc is particularly well known to have this role, while it may also serve to stabilize biological structures and to form crosslinks. The ion Zn^{2+} bears some resemblances to Mg^{2+}, although it forms complexes to a greater extent. It is not surprising therefore that Mg^{2+} also acts as a Lewis acid, although it is a weaker Lewis acid than Zn^{2+}. Weak effects and strong effects may be needed under different circumstances.

Calcium, in contrast to magnesium, does not have an important function as an enzyme activator, in accord with its different distribution. It is very important, however, in the control and triggering of biological processes such as muscle contraction and the release of various chemicals, including hormones, defence chemicals and neurotransmitters. This occurs when, in response to some stimulus, the normal selectivity of the cell membrane or the membranes of internal organelles breaks down, and calcium ions are allowed to enter the cell. These bind to specific sites and trigger certain reactions.

Both the IA and IIA cations have important roles in the neutralization of negative charge on various organic polymers, and in the stabilization of certain structures. Thus K^+ and Mg^{2+} stabilize ribosomes, while the binding of Ca^{2+} may stabilize enzymes against denaturation, such as thermolysin which functions at high temperatures.

The IA cations Na^+ and K^+, as noted earlier, are involved in control processes, through the existence of concentration gradients. They are not usually regarded as enzyme activators, except for the Na^+,K^+-activated adenosinetriphosphatase of the sodium pump, which is responsible for the translocation of these two ions across membranes and hence for the maintenance of their selective distribution against concentration gradients. However, the role of K^+ as an enzyme activator is probably not fully appreciated; it is likely to function mainly through binding and the induction of necessary conformational changes in the enzyme.

These roles are summarized in Table 3 for convenience. They will be discussed in greater detail and illustrated in subsequent sections.

Table 3 Roles for Metals in Biology

Metal	*Metal–ligand interaction*	*Function*
Na^+, K^+	Very weak	Osmotic balance Charge neutralization Gradients and control mechanisms Structure stabilization (K^+) Enzyme activation (K^+)
Mg^{2+}, Ca^{2+}	Medium	Enzyme activation (Mg^{2+} behaves as a weak Lewis acid) Structure stabilization Trigger effects (Ca^{2+})
Zn^{2+}, Ni^{2+}	Strong	Lewis acids Structure stabilization (Zn^{2+})
Transition metals	Very strong	Redox catalysts
Fe, Cu		Dioxygen carriers

62.1.1.3 Analysis

It would be inappropriate to discuss the subject of metal ions in biology without making reference to the essential question of analysis. Analysis is necessary to establish the concentration

levels and site of location of metals in an organism, and ultimately for the determination of the stoichiometry of metal–ligand binding in a biological molecule. A number of techniques are available which work well for simple solutions of inorganic compounds, but which require considerable attention before they may be applied to the analysis of metals in complex biological matrices. Furthermore, measurements of trace levels of metals may present a major challenge in excluding contamination by adventitious metal from various sources. Thus, plastic tips used in micropipettes are often contaminated with cadmium and iron, and should therefore be washed with nitric acid before use.

Certain techniques such as neutron activation analysis and stable isotope dilution analysis offer very powerful and sensitive methods for the determination of trace metals, but involve considerable effort and access to extensive facilities and so are not suited for routine laboratory determinations. However, they have been used to determine trace metal levels accurately in homogeneous biological materials, which are now used as reference materials for other techniques.

In stable isotope dilution techniques, an enriched stable isotope is added to the sample to be analyzed. Comparison of the amount of that isotope relative to another isotope of the element in a sample then allows the amount of the element in that sample to be determined. The normal relative amounts of the two isotopes have been altered by the addition of the known amount of the enriched isotope, so allowing the calculation. The technique cannot be used where an element does not have two stable isotopes and so elements such as Na, Mn and Co are excluded. A considerable advantage results from the fact that the determination involves the ratio of two isotopes, in that quantitative recovery of an element is not necessary.

Neutron activation analysis involves the exposure of the sample to high neutron flux densities in a nuclear reactor, but is a very sensitive method for certain metals, as illustrated by the following data on detection limits (ng): Fe, 3200; Zn, 420; Co, 12; Ni, 7; Na, <0.1; Cu, 0.035; Mn, 0.001.

The techniques of atomic absorption and emission spectroscopy are probably the most widely used. Detection limits ($\mu g\ ml^{-1}$) found in conventional flame spectroscopy are Zn (0.002), Mn, Cu (0.005), Ni, Fe (0.01), Co (0.02), Mo (0.6) for the most sensitive line. These limits may be improved by preconcentration of the metal by extraction with solvents containing chelating agents. Such extraction techniques also allow the removal of the metal from the biological matrix, which otherwise results in non-specific background absorbance. The use of carbon furnace techniques extends the detection limits 10-fold. The development of heating programmes for the furnace with appropriate drying, charring and atomization steps may allow the loss of the biological matrix before the atomization, but this does not usually occur, and background correction is particularly important for this technique as well as the flame technique. Nevertheless, time spent on the development of the heating programme pays dividends in the effectiveness of the technique. Current improvements in AA spectroscopy are largely concerned with background correction.

The somewhat neglected technique of stripping voltammetry may in some cases offer considerable advantages over atomic absorption spectroscopy, both in sensitivity and in coping with various interference problems. In this technique, the metal ions present in solution are first reduced at a controlled potential, usually with a hanging drop mercury electrode, while the second stage involves anodic dissolution or stripping in which the metal is oxidized. The resulting stripping voltammogram shows peaks whose areas are generally proportional to the concentrations of the corresponding metal ions. Standards are required and are submitted to identical treatment.

Ion-sensitive electrodes are finding increasing use and are superseding atomic absorption techniques in certain cases, partly because of the limited requirements of these electrochemical methods. Electrodes for Na^+, K^+ and Ca^{2+} are particularly important, but suffer from the drawback of slow response time. They may be of less value, therefore, in continuously monitoring changes in concentration levels with time. Thus Ca^{2+}-sensitive electrodes have a detection limit of about 10^{-8} mol dm^{-3}, but a response time of about 2 s.

Finally it should be noted that while classical methods for analysis tend to be little used, there are certain colorimetric methods for calcium which are of value. Thus, determinations with arsenazo III involve a detection limit of 10^{-7} mol dm^{-3}. Calcium may also be determined using the photoproteins aequorin and obelin, which emit light on interaction with Ca^{2+} and have detection limits around 5×10^{-8} mol dm^{-3}. These methods have had some interesting *in vivo* applications.

62.1.1.4 Some General Comments

Most of the topics reviewed in this chapter will be concerned largely with the structure, spectroscopic properties and reactivity of metal ions complexed to biological ligands, notably

proteins. Inevitably this discussion presents a static view of the subject of 'inorganic biochemistry'. In practice, of course, the biological chemistry of metal ions involves a mobile picture, in which elements are taken up, move between cells and also between organelles in cells, in a controlled way through the involvement of specific uptake and transport processes. The goal of inorganic biochemistry is a full understanding of the behaviour of metals (and non-metals) in their natural biological environment. In a few cases, an approach is being made to this problem, notably in the case of iron. In other cases, the increasing use of NMR techniques could lead to a greater appreciation of the *in vivo* function of metal ions.

The arrangement of material in this section presented some difficulties. In an introductory text, there are obvious merits in emphasizing the metal ion, and in presenting a discussion of the biochemistry of each metal ion or groups of metal ions in turn. However, the presence of functional similarities between many enzymes having different metal centres means that a more useful classification would have involved that of function. In practice, a compromise position has been taken in which a brief account of the biochemistry of each metal will be presented, followed by a fuller discussion of certain essential topics.

The literature of inorganic biochemistry is expanding rapidly. A number of books are available,[1-12] together with several review series.[13-16] Some general review series[17-19] occasionally have volumes devoted to topics of interest to inorganic biochemists. Series devoted to specialized aspects of the subject will be noted as appropriate. Analytical methods have been reviewed.[20,21]

62.1.2 SODIUM AND POTASSIUM

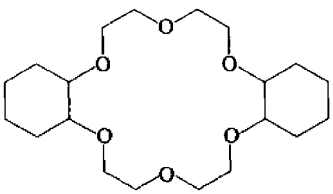
Two aspects of the biological chemistry of Na^+ and K^+ (and of Mg^{2+} and Ca^{2+}) are dominant, namely their abundance and their selective distribution.[22] The fact that K^+ is concentrated in the cytoplasm while Na^+ is rejected by the cell is central to an understanding of their biological roles. These cation concentration gradients are only maintained by the expenditure of energy through the hydrolysis of ATP, and by the presence of appropriate control systems in the membranes which incorporate binding sites that can distinguish between Na^+ and K^+. They are linked to many aspects of cellular physiology, and their importance is emphasized by the fact that, in resting cells, the maintenance of these gradients consumes a major part of the energy utilized by the cell.[23] Indeed, one half of the basal metabolic rate in man (7100 kJ d^{-1}) is expended in pumping Na^+ out of cells. It must be emphasized that a wide range of cellular membranes[24] participate in ion transport, and that the resulting gradients are utilized in a range of transport processes. The Na^+ gradient is utilized in amino acid transport in red blood cells and other cells, and in sugar transport in the intestine. Nerve cells have specific channels for Ca^{2+} and Na^+.

As noted in Section 62.1.1, the alkali metal cations bind ligands weakly and can be regarded as aqua ions in solution, as appropriate for their function as diffusible ions. Indeed, a range of techniques have shown that the alkali metals in the cell can be considered as aqua ions, although a certain percentage will be bound to various sites. It should be noted, therefore, that EXAFS data for potassium in 0.2 mol dm^{-3} [K^+] in aqueous solution and for K^+ in frog blood cells (of similar concentration) suggest that the K^+ is not present in the same environment in the two cases. Thus it may be incorrect to assume that potassium in the cell can be regarded as a simple aqueous solution.[25] A second example involves members of the genus *Halobacterium*, which grow in media of high salinity such as 3.5 mol dm^{-3} NaCl, and have a high intracellular ion content of about 4 mol dm^{-3} K^+ and 1.5 mol dm^{-3} Na^+. The use of NMR techniques has shown the presence of bound and free intracellular Na^+, Rb^+ and Cs^+. The last two cations replace K^+, which cannot be readily studied by NMR techniques.

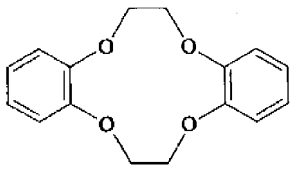
62.1.2.1 Selective Binding of Sodium and Potassium Cations

Complexes of the alkali metals are discussed in Chapter 23, Volume 3, while a comprehensive review of material published up to 1978 is also available.[26] These complexes usually involve oxygen donor ligands, which may be neutral or negatively charged. The selective binding of Na^+ and K^+ by such ligands is a particularly appropriate background topic to their biological chemistry. Such selectivity is shown[27] by ligands having cavities as the metal-binding site. In a crude sense, selectivity is determined by matching ionic radius to the cavity radius. Examples include the crown ethers, cryptands[28] and a range of naturally occurring antibiotics. Some non-cyclic ethers also bind selectively.[27]

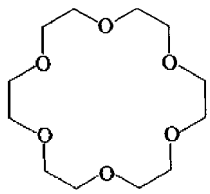
Thus K^+ is bound selectively compared to Na^+ by 18-crown-6 and [2.2.2]cryptand, while the reverse is true for dicyclohexyl-16-crown-5 and [2.2.1]cryptand. These ligands are shown in Figure 3. The cation Na^+ misfits in 18-crown-6 due to its smaller size. The cryptands form complexes of greater stability than do the crowns, and also show greater selectivity as they have a 'three-dimensional' cavity. These ligands have a flexible structure that allows the stepwise replacement of aqua groups on the metal ion.



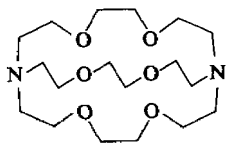
Dicyclohexyl-18-crown-6



Dibenzo-12-crown-4



18-Crown-6



[2.2.2]Cryptand

Figure 3 Some typical crowns and cryptands

The antibiotics are compounds secreted by microbes that enhance the permeability of membranes to cations. One class functions by binding a metal to give a liposoluble complex that can then pass across the membrane. Examples are valinomycin, a cyclic peptide that binds K^+ selectively, and monensin which binds Na^+. These too are oxygen-donor ligands, and will be discussed in the following section. They function as antibiotics because they allow the concentrations of a cation across membranes to become equalized, and so cause the collapse of the membrane potential.

62.1.2.2 Transport of Cations

Biological membranes present a barrier to the free transport of cations, as the hydrophilic, hydrated cations cannot cross the central hydrophobic region of the membrane which is formed by the hydrocarbon tails of the lipids in the bilayer. Specific mechanisms thus have to be provided for the transport of cations, which therefore allow for the introduction of controls. Such translocation processes may involve the active transport of cations against the concentration gradient with expenditure of energy *via* the hydrolysis of ATP. These ion pumps involve enzyme activity. Alternatively, facilitated diffusion may occur in which the cation is assisted to cross the hydrophobic barrier. Such diffusion will follow the concentration gradient until concentrations either side of

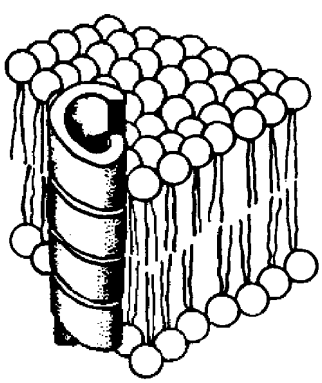


Figure 4 Schematic representation of gramicidin channels in membranes

the membrane are equal. This process requires the participation of an 'ionophore' or ion carrier, which may either be a carrier or a channel former. As described earlier, the carrier forms a liposoluble complex with the cation, which is able to cross the membrane. The ionophore may be negatively charged and so give a neutral complex, or it may be a neutral species and so form a charged complex. In the latter case the complex will require a permeant anion to move with it. The channel-forming ionophores are usually proteins that form helical channels in the membrane, which are water filled and thus allow the transport of hydrophilic species, provided the channel spans the membrane. This is illustrated in Figure 4 for gramicidin.

A great deal of work on model transport systems has been carried out using cyclic ethers and cryptands[27] of some complexity. Often selectivity in binding is not related to selectivity in transport, as the best ionophores are often large ones that wrap around the cation, so shielding it effectively from the hydrophobic bilayer. Such large ionophores do not bind cations selectively. The antibacterial activity of crown ethers is related to their ability to transport K^+.[29]

62.1.2.2.1 Some ionophoric antibiotics

Table 4 lists some antibiotics that function as ionophores, including some that bind Group IIA cations. Ionophores may be classed as channel formers or carriers by several approaches. A carrier ionophore is dependent on membrane fluidity and so cannot function below the transition temperature of the phospholipids in the membrane, as these are now 'frozen'. The channel formers are much less dependent on membrane fluidity. A channel-forming ionophore cannot function if it fails to span the membrane, and so if an ionophore ceases to function in thicker membranes then it is probably a channel former. The kinetics of ion transport may provide a good indication of the type of ionophore. If an ionophore functions at a rate of more than 10^4 ions s^{-1} then it must be a channel former, as this level of ion flux cannot be provided by the diffusion of a carrier complex across the membrane.

The linear peptide gramicidin A (15 residues) dimerizes in biological and synthetic membranes in a head-to-head manner[30] to give channels of about 5 Å in diameter and 32 Å in length. These channels are specific for alkali metal cations, and show high transport rates, *e.g.* 10^7 Na^+ ions s^{-1}, a value close to the ion fluxes found for the Na^+ channel of nerve cells. Each structural unit appears to contain two channels, each of which contains two binding sites for cations.

Binding of IA cations to gramicidin results in conformational changes to give a channel length of 26 Å and a diameter of 6.8 Å.[31] The use of ^{23}Na NMR techniques confirms[32] that Na^+ binds to the gramicidin A dimer at well-defined sites, with binding constant $K = 4$ dm^3 mol^{-1}. These are suggested to be outer sites associated with the entrance to the channel. Binding of Na^+ involves partial dehydration, which is probably necessary in view of the small size of the channel. The channels are blocked by Ca^{2+}.

The interior of the channel is lined with peptide carbonyl oxygen atoms, which interact electrostatically with the water in the channel and also with water beyond the end of the channel.[33] The water structure in the channel will be affected by the presence of cations.

The cations probably interact with the peptide carbonyl groups. This may require a widening of the channel, which will result in a shortening of its length, as noted earlier.

Synthetic peptides such as $(Leu\text{-}Ser\text{-}Leu\text{-}Glu)_{12}$ act as channels in artificial membranes, and reproduce the hydrophobic exterior (from leucine side chains) and hydrophilic interior (from serine hydroxyl groups) characteristic of natural channel formers.

While gramicidin and other channel formers can show high transport rates, they do not show the high selectivity that characterizes natural channels. There is much interest at present in a class of proteins called porins, which form natural pores in the outer membranes of Gram-negative bacteria. Several different porin proteins have been isolated from *Escherichia coli*. These form water-filled channels of various sizes in membranes. Thus the proteins OmpC and OmpF seem to be cation-specific channels while other proteins give larger diameter channels that seem to be specific for anions.[34,35]

The carrier ionophores fall into two main groups: the monobasic carboxylic acid derivatives of polyethers and the neutral macrocycles. An example of the latter class is valinomycin, a cyclic dodecadepsipeptide whose structure is shown in Figure 5, and which is selective for K^+. The conformation in solution is flexible and solvent dependent. X-Ray studies show that the K^+-valinomycin complex contains the dehydrated cation with the ester carbonyl groups directed inwardly towards it giving octahedral geometry. IR studies show that the Na^+-valinomycin complex has non-equivalent carbonyl groups, reflecting the misfitting of the smaller Na^+ ion.

Table 4 Some Ionophoric Antibiotics

Ionophore	*Exchange*	*Mode*	*Ref.*
Polyether monocarboxylates			
Carriomycin		Carrier	1
Ionomycin dicarboxylate	Ca^{2+}	Carrier	2
Dianemycin	M^+	Carrier	3
Monensin	Na^+/H^+	Carrier	4
Nigericin	K^+/H^+	Carrier	5
Lasalocid A (X573A)	Ca^{2+}	Carrier	6
Septamycin		Carrier	7
K41 (A32887)	K^+	Carrier	8, 9
6016	K^+	Carrier	10
A23187	Ca^{2+}	Carrier	11
Neutral molecules			
Beauvericin (hexadepsipeptide)	Ca^{2+}	Carrier	12
Valinomycin (cyclic peptide)	K^+	Carrier	13
Nonactin (macrotetrolide)	K^+	Carrier	14
Enniatin B (cyclohexadepsipeptide)	K^+	Channel	15
Gramicidin (linear peptide)	M^+	Channel	16
Trichotoxin		Channel	17
Alamethicin		Channel	17, 18
Suzukacillin		Channel	17, 19

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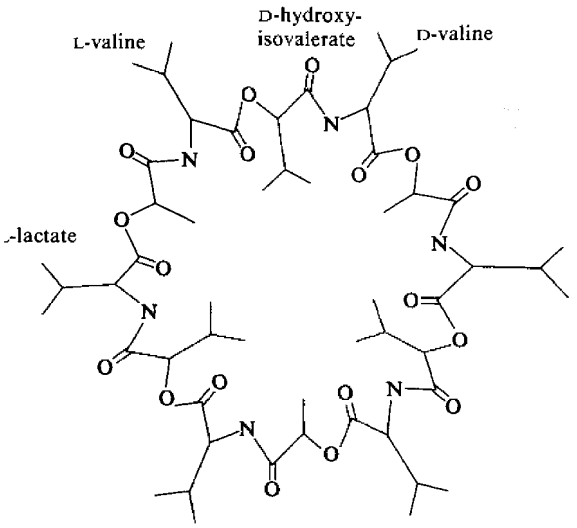
Note: The latest volume (19) in the series 'Metal Ions in Biological Systems', ed. H. Sigel, Dekker, New York, 1985, is devoted to antibiotics and their complexes.

Also in Figure 5 are shown the actins. Nonactin provides a cavity appropriate for K^+, the ligand wrapping around the cation.

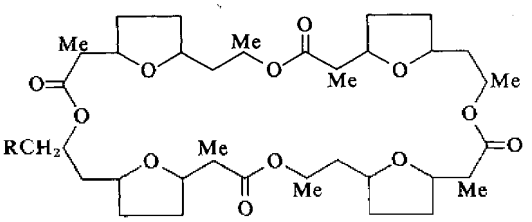
A range of cyclic peptide analogues of valinomycin have been synthesized having proline and valine residues. For PV [*cyclo*(-Val-Pro-Val-Pro-)$_3$], PV-10 [*cyclo*(-Pro-Val-Pro-Val-)$_2$-Pro-Val] and PV-8 [*cyclo*(-Pro-Val-Pro-Val-)$_2$] the preference for K^+ over Na^+ was 700, 5 and <1 respectively, showing how selectivity depends upon the ring size.[36]

The polyether monocarboxylate ionophores in general seem to take up conformations *via* hydrogen bonding involving the carboxylate group, which provide a cavity for the cation. Examples are monensin, which binds Na^+, and nigericin, which is selective for K^+. Dianemycin binds IA cations without discrimination, reflecting its greater flexibility.

Ionophores X-573A (lasalocid A) and A23187 are usually regarded as carriers for Ca^{2+}, but they will bind Na^+. If formed from non-polar solvents the Na^+/X-573A complex is dimeric, but if prepared in methanol it is monomeric, in which the Na^+ is complexed by five oxygen donor atoms and the sixth position is filled by water. In the dimer, the water is absent and the coordination of the cation is completed by dimer formation.[37] These results suggest that monomeric Na^+-



Valinomycin



R = H Nonactin
R = Me Monactin

Figure 5 Some ion carriers (see also A23187 in Figure 2, p. 547)

ionophore complexes are formed in the polar exterior of the lipid bilayer but they move across the lipid bilayer as dimers.

The use of ionophores to control the distribution of cations across membranes represents an important technique in cell physiology.

62.1.2.2.2 The sodium pump: (Na^+, K^+)-ATPase

Sodium and potassium ion-activated adenosine triphosphatase is a complex, membrane-bound enzyme that catalyzes the transport of three sodium ions out of the cell and two potassium ions into the cell with associated hydrolysis of MgATP. If cells are cooled to 0 °C, then active transport ceases and the membrane behaves as a normal Donnan membrane in which the flow of ions is towards equalization of concentrations inside and outside the cell. It is possible to envisage in general terms how enzymatic function can be linked to transport of cations. The enzyme binds and releases Na^+ and K^+ at certain stages in the reaction in response to changing affinities, while conformational or other changes taking place in the enzyme result in the cations being released at the opposite surface of the membrane from which they were taken up. Aspects of the sodium pump have been reviewed many times.[24,38–44]

The enzyme has been purified from a number of membrane preparations. In all cases, the enzyme consists of two different polypeptides, with molecular weights about 100 000 and 50 000, designated the α- and β-peptides respectively. The α-peptide is the catalytic peptide, and contains the phosphorylation site. It undergoes phosphorylation at the β-carboxyl group of an aspartic acid residue from ATP in the presence of Mg^{2+} and Na^+. The phosphatase reaction requires K^+. The α-peptide also contains the binding site for the cardiac glycoside inhibitors such as ouabain. The β-peptide is a glycopeptide whose function is uncertain. Various binding and chemical crosslinking experiments support the proposition that the ATPase is a dimer made up of two pairs of the α- and β-peptides. However, there is some evidence that the monomeric complex containing only one α-peptide and one β-peptide exhibits full enzymatic activity.[45]

Most work has been carried out on the larger peptide. Controlled hydrolysis with trypsin in the presence of K^+ or Na^+ gives different results for the loss of ATPase activity. The simple interpretation of these experiments is that the enzyme exists in two different conformations in the presence of these cations. The α-peptide is known to span the membrane, and so can provide a pathway across it for cations. The results of hydrolysis with trypsin have been used to identify the portions of the peptide that span the membrane.[46] These portions will not be subject to cleavage, and will therefore be at least 26 residues in length, the minimum length necessary to span the membrane. Five peptides have been identified by this technique, all of which contain a very high frequency of hydrophobic amino acids, and appear to represent the membrane-spanning

segments of the α-polypeptide. Three of these small peptides contain 30–40 residues, one contains 50 and the other 70. The last of these probably represents two membrane-spanning helices, giving a total of six. This has allowed a model to be set up for the α-polypeptide. If it transverses the membrane six times then this will require some 160 amino acid residues and give a cylinder 26 Å in diameter and 40 Å in height. This leaves some 840 residues outside the membrane,[47] so allowing an estimate of the volume of the peptide. The model is shown in Figure 6, which is consistent with other published data. The K^+ ions (•) are drawn to scale, and provide a useful perspective.

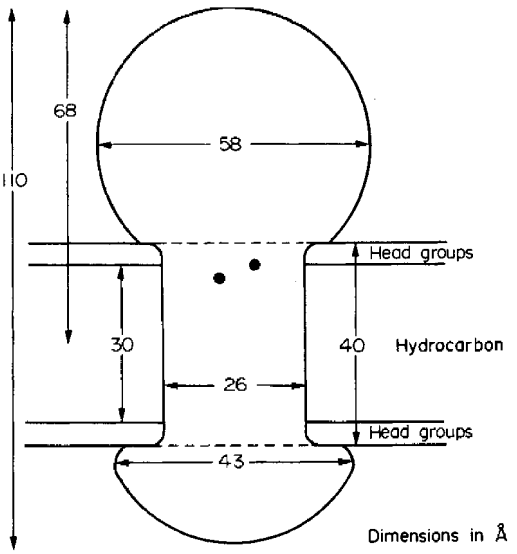


Figure 6 Proposed structure for the polypeptide of the sodium pump (reproduced with permission from *Biochemistry*, 1984, **23**, 888, American Chemical Society, Washington, DC)

Other studies on the α-polypeptide have implicated two tyrosine residues and an arginine residue in the active site, while there also appear to be exposed SH groups, whose alkylation results in loss of enzymatic activity. The residues that make up the ATP-binding site have been labelled by photoaffinity techniques, using as an ATP analogue the Cr^{III} complex of 3′-*O*-[3-[(4-azido-2-nitrophenyl)amino]-3-tritiopropionyl]adenosine 5′-triphosphate. When photolyzed, the α-polypeptide was tagged at the active site. Proteolytic digestion gave certain fragments which were radioactively labelled, and shows that amino acids at least 200 residues beyond the site of phosphorylation are involved in the active site.[48]

The orientation of the β-polypeptide has been explored by the use of lipophilic affinity labelling reagents generated photochemically inside the membrane. This shows the region of the polypeptide embedded in the lipid bilayer. The probe *O*-hexanoyl-3,5-diiodo-*N*-(4-azido-2-nitrophenyl)tyramine undergoes photochemical conversion into the reactive nitrene, and has been used to label the (Na^+, K^+)-ATPase from *Bufo marinus* toad kidney. This shows that the β-polypeptide is also a transmembranous polypeptide,[49] a view that is in accord with immunochemical evidence.[50]

A full consideration of the mechanism of the sodium pump requires an account of the role of the lipid, the binding sites for Na^+, K^+, Mg^{2+} and ATP, the mechanism of hydrolysis of ATP and the way in which this is coupled to the transport of the cation. In addition it should be noted that the enzyme also functions as a K^+-dependent phosphatase, a reaction usually studied with *p*-nitrophenyl phosphate as substrate. Studies with inhibitors have been informative, notably with ouabain and with vanadate. Ouabain binds at one site per pump and so has been of value in quantitatively defining the enzyme in various preparations.

Lipid-free (Na^+, K^+)-ATPase is incapable of hydrolyzing ATP or *p*-nitrophenyl phosphate. The precise role of the lipid and the specificity for the lipid have not yet been determined. The addition of lipid to the delipidated enzyme brings about conformational changes, with phosphatase activity regenerated before ATPase activity.[51] It seems evident that the lipid will affect the conformation of the enzyme and determine membrane fluidity, which is relevant to conformational change.

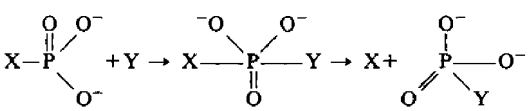
The question of binding sites for the monovalent cations is an extremely complex one and no scheme is universally accepted at the present time. These studies have been complicated by the presence of other transport processes such as K^+/K^+ exchange, Na^+/Na^+ exchange, and uncoupled Na^+ efflux which occur under certain conditions. There must be intracellular Na^+ sites and extracellular K^+ sites, but in addition there are extracellular and intracellular sites for Na^+ and K^+ respectively as shown by these alternative transport modes. Evidence has been presented for three internal sites[52] for Na^+ and two extracellular sites[53] for K^+. This fits neatly with the observed stoichiometry of $3Na^+/2K^+/1ATP$. An important aspect of this work involves the use of vesicles incorporating the (Na^+, K^+)-ATPase which have either right-side-out or inside-out orientation, so that access to one side of the membrane may be studied in isolation from the other.[54]

Li^+ may bind at the Na^+ site with activation[42] while K^+ binds with inhibition. For these internal Na^+ sites, $K_m\ (Na^+) = 1.23$ mmol dm^{-3} and $K_I\ (K^+) = 4.5$ mmol dm^{-3}. Both high and low affinity sites exist for K^+; for the high affinity sites $K_m\ (K^+) = 0.08$ mmol dm^{-3} and $K_I\ (Na^+) = 14.3$ mmol dm^{-3}, thus showing good discrimination between K^+ and Na^+. The low affinity sites have $K_m\ (K^+) = 1.2$ mmol dm^{-3} and appear to be involved in the phosphatase reaction; Na^+ binds with inhibition [$K_I\ (Na^+) = 4.5$ mmol dm^{-3}]. Other Group IA cations activate at the K^+ sites: thus there is evidence for two sites for Rb^+ per ouabain site.

These sites for M^+ cations have been explored by the use of NMR probes such as $^{205}Tl^+$ and $^7Li^+$, while distance measurements have been carried out with Mn^{2+}. It is possible, of course, that these M^+ cations bind both to K^+ and Na^+ sites. The identity of the binding site is usually confirmed by measuring the effect of added Na^+ and K^+ on the binding of the NMR active probe and hence determining the relative affinities of Na^+ and K^+ for the site. Comparison with published data on the available sites allows the site at which the probe is bound to be identified. Such approaches suggest that Li^+ binds[55] at the low affinity sites for K^+, and also that these sites are 7.2 Å from the Mn^{2+} site. The Tl^+ cation activates at K^+ sites and inhibits at Na^+ sites. Binding of Tl^+ at the Na^+ sites has been characterized,[56] while the Tl^+–Mn^{2+} distance is 4.0 and 5.4 Å in the absence and presence of phosphate. Thus the Na^+ transport site is close to the site for ATP hydrolysis in the (Na^+, K^+)-ATPase, while the low affinity sites for K^+ are no more than 12.6 Å from the Na^+ transport site. The geometry of the active site is starting to be understood.

For the ATPase activity of the enzyme, Mg^{2+} is required. Kinetic studies confirm that MgATP is the substrate and that while free ATP binds to the enzyme it inhibits activity. It appears that MgATP binds at high and low affinity sites, with K_m values about 3 μmol dm^{-3} and 0.2 mmol dm^{-3} respectively. For phosphorylation of the enzyme, saturation of the high affinity site is sufficient for maximum activity. Binding at the low affinity sites inhibits ADP/ATP exchange and may represent a modulator role for these sites. This low affinity site may be the site for the substrate in the K^+-phosphatase reaction.

The activating effect of Mg^{2+} upon the cleavage of the phosphoryl group from the ATP could reflect the enhancement of an S_N2 reaction at phosphorus by electron withdrawal and charge neutralization *via* coordination to the metal (equation 1). Support for an S_N2 mechanism comes from a consideration[57] of the inhibition by vanadate. Coordination of the transferable phosphoryl group would inhibit the S_N1 mechanism.

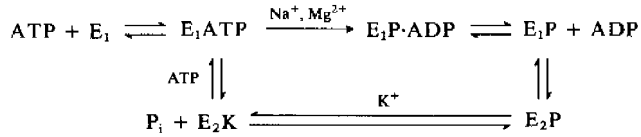


(1)

Mg^{2+} also has a role as a regulator of enzymatic activity. ESR studies[40] using Mn^{2+} have shown the presence of one tight binding site per 250 000 relative molecular mass of protein, and additional binding capacity for 24 ± 3 Mn^{2+} ions of lower affinity. The latter sites are associated with the membrane phospholipid. Removal of the lipid results in the loss of the weak binding sites for Mn^{2+} but has no effect on the tight Mn^{2+} site. NMR relaxation data indicate that there are four exchangeable protons in the inner coordination shell of the enzyme-bound Mn^{2+}.

As noted earlier, studies with inhibitors have been of great value. One mole of ouabain binds per enzyme complex and inhibits all enzyme functions. It provides a convenient marker for the extracellular surface of the enzyme. Oligomycin inhibits the (Na^+, K^+)-ATPase but not the K^+-phosphatase reaction. It stimulates the ADP/ATP exchange reaction and this led to the postulate for two phosphoenzymes in the reaction scheme. Anomalous kinetic behaviour for (Na^+, K^+)-ATPase, over some years, was eventually recognized[57] to be due to a vanadate impurity in ATP, which binds with high affinity to the low affinity ATP site and with low affinity to the high affinity ATP site. In accord with this, vanadate effectively inhibits the K^+-phosphatase

reaction. It inhibits the ATPase with $K_I = 0.5\ \mu mol\ dm^{-3}$, and may well be a regulator for its activity. Vanadate has striking pharmacological effects on cardiac contractility, blood pressure and urine flow.[58] One complication is that in red blood cells, vanadate, which is taken up by a phosphate transport system, is reduced to the vanadyl ion VO^{2+} by intracellular glutathione.[59,60] Vanadyl ion is probably the major form of intracellular vanadium, and it appears to be a relatively potent inhibitor of membrane-bound kidney (Na^+, K^+)-ATPase, producing nearly complete inhibition at a concentration of less than 5 $\mu mol\ dm^{-3}$ in some highly purified preparations of the enzyme.[61]



Scheme 1

The reaction sequence[62,63] is summarized in Scheme 1. The enzyme is phosphorylated in the presence of Na^+ and Mg^{2+} to give a phosphoenzyme E_1P, which can undergo conformational change to give another phosphoenzyme E_2P. There is good evidence for a reaction sequence containing two phosphorylated enzyme states.[64,65] Species E_2P then undergoes dephosphorylation in a K^+-dependent process, and E_2 is converted back to E_1 in a slow conformational change catalyzed by the binding of ATP at a low affinity site.

A number of schemes involving 'half of the sites' activity and flip-flop mechanisms have been put forward in an endeavour to accommodate the dimeric nature of the enzyme and the transport of the cations. Mechanisms requiring large conformational changes seem unlikely in view of experiments in which the attachment to the pump of an antibody which would hinder rotation had little effect on transport.[66] The fact that the α-polypeptide spans the membrane suggests that this should be incorporated into the transport scheme. Active transport could be achieved if the ions are driven by oscillations in the boundary of the pore. This requires small conformational changes lateral to the transported ion, so that a helical section of the channel, present in the π-form with 4.4 residues per turn, is propagated along the channel. This channel is large enough to allow Na^+ but not K^+ to pass through. The K^+ cannot be accommodated by the π-helix, but is suggested[67] to be transported by an interhelical channel. Furthermore, if there are three channels for transport of Na^+, then an array of three helices will create two interhelical channels for K^+, so accounting well for the $3Na^+/2K^+$ stoichiometry. However, further structural information on the sodium pump is required before these ideas can be assessed fully.

62.1.2.2.3 Transport in microbes and other systems

The Na^+ gradient established by the (Na^+, K^+)-ATPase is utilized in the transport of a number of solutes into animal cells *via* Na-solute cotransport or symport.[68] This is well known for glutamate. Renal Na^+ cotransport systems for mono- and di-carboxylic acids and for various amino acids have been functionally reconstituted in proteoliposomes. These transport systems are polypeptides solubilized from brush border membranes of renal proximal tubules. The establishment of Na^+ gradients (high Na^+ outside) resulted in increases in concentrations of substrate inside the proteoliposomes.[69]

Prokaryotic organisms have developed a number of transport mechanisms for the extrusion of sodium ions against a concentration gradient. In *Escherichia coli* sodium efflux is linked to proton uptake and is independent of internal ATP, *i.e.* the cell uses a sodium/proton antiporter.[70,71] In contrast in *Streptococcus faecalis*,[72] sodium efflux involves an ATP-driven sodium-translocating ATPase, while in *Halobacterium halobium* the protein halorhodopsin has been postulated to catalyze the coupling of Na^+ extrusion to light.[73]

The sodium gradient in the methanogen *Methanococcus voltae* is exploited in the transport of isoleucine as a positively charged complex,[74] where concentration gradients over 100 can be achieved. It is noteworthy that the methanogens represent one of the few cases where a growth requirement for Na^+ can be shown.[75,76]

In general, however, in prokaryotes the function of Na^+ in the cotransport of solutes is taken over by H^+. A proton gradient is set up across the plasma membrane by the membrane ATPase,

which has some biochemical similarities to the (Na^+, K^+)-ATPase, although it is physiologically analogous to the proton translocating ATPase of mitochondria. The similarity with the (Na^+, K^+)-ATPase is demonstrated by its inhibition by vanadate, which prevents the formation of the proton gradient and membrane potential in *Neurospora crassa*, *Saccharomyces cerevisiae* and *Mycobacterium phlei*.[77] The transport of nutrient solutes is linked in may cases to this proton gradient. Cationic metabolites such as lysine are then transported by a uniport mechanism. Uncharged metabolites such as isoleucine would permeate by proton symport, while anionic species would also permeate by proton symport.[78] The melibiose system of *E. coli* is unique in its cation coupling. It is capable of using H^+ or Na^+ depending on the substrate. Indeed in mutant cells Li^+-melibiose cotransport can occur.[79]

The uptake of potassium by microorganisms has been well studied. In the case of *E. coli*, kinetic investigations on different strains have demonstrated the presence of three or four transport systems. The presence of inducible pathways with widely different K_m values for binding K^+ allows the cell to accumulate K^+ to a constant level under different environments. These transport pathways include those linked to the proton circuit and an example linked to a pump and ATP hydrolysis. Thus the Kdp system is a high affinity pathway with $K_m = 2$ mol dm^{-3}, and involves three proteins in the inner membrane of *E. coli*, including a K^+-stimulated membrane ATPase. The KHA (*i.e.* K^+-H^+ antiport) path is driven by proton motive force, while the low affinity system TrKA depends on both ATP and the proton motive force.[80,81,82] *S. cerevisiae* accumulates K^+ by K^+/H^+ exchange.[83] Potassium transport may thus be used to control intracellular pH.

The water mould *Blastocladiella emersonii* generates a transcellular electrical current. It appears that K^+ is actively accumulated in a primary transport process that may exchange K^+ for H^+, and that K^+ leaks passively outwards through the K^+ channel.[84]

As a final example, it should be noted that in the presence of valinomycin, K^+ is taken up by mitochondria to compensate for the H^+ lost in forming the proton gradient. This work confirms the ratio of four K^+ taken up per pair of electrons passing the energy-conserving site and so is equivalent to the H^+/site ratio.[85] The protein responsible for K^+/H^+ antiport has been identified.[86] Other potassium transport processes have been described.[87]

62.1.2.3 Biological Roles for Sodium and Potassium Ions

The exploitation of the Na^+ gradient across membranes in the transport of solutes into the cells has been emphasized. These gradients are exploited in other ways as well. Thus alkalophilic *Bacillus* whose optimal growth pH is between 9 and 11 swim vigorously at high pH,[88] because the flagellar motors are powered by the transmembrane electrochemical potential gradient of Na^+. Influx and efflux of Na^+ into and from fertilized sea urchin eggs vary systematically during fertilization and subsequent cell divisions.[89] This may be associated with use of the Na^+/H^+ symport to vary the intracellular pH and hence control the metabolism of the eggs and in particular the stimulation of protein synthesis.

Other areas of specific interest include the role of the IA cations as charge carriers in the transmission of nerve impulses, as stabilizers of a variety of structures, and as activators of a large number of enzymes. The first topic is outside the scope of this chapter, although progress is being made in the study of metal-selective channels in nerve cells.

62.1.2.3.1 Alkali metal ions as enzyme activators

A very large number of enzymes show an absolute requirement for a monovalent cation for catalytic activity, and for most of these K^+ is most effective.[90,91] Usually Na^+ is inactive but a small number of enzymes [apart from (Na^+, K^+)-ATPase] have a specific requirement for Na^+, such as oxaloacetate decarboxylase.[92] The oxidation of NAD-linked substrates by the aerobic marine bacterium *Alteromonas haloplanktis* requires the presence of Na^+.[93] Monovalent ions other than Na^+ can usually replace K^+ but with lowered activity. The Rb^+ cation usually substitutes quite effectively, but there has been much interest in replacing K^+ with Tl^+, in order to exploit the NMR properties of the latter cation. Tl^+ sometimes causes inhibition, as it binds more strongly than K^+ and sometimes to additional sites, reflecting its 'soft' chemical character. On occasions Tl^+ may activate an enzyme more effectively than the native K^+. Some examples of enzymes activated by monovalent cations are given in Table 5.

Table 5 Some Enzymes Requiring K^+ or Na^+ for Activation

Enzyme	*Cation requirement*	*Comments*	*Ref.*
Pyruvatekinase	K^+, Mg^{2+}	$K^+ > NH_4^+ > Tl^+ > Rb^+$	1
Phosphofructokinase	K^+		2, 3
Carbamoyl-phosphate synthetase	K^+, Mg^{2+}		4
Aspartokinase	K^+	*Escherichia coli*	5
		Bacillus spp.	6
Acetic thiokinase	K^+	Na^+ inactive	7
Pyruvate carboxylase	K^+		8
Formyltetrahydrofolate synthetase	K^+	Protein subunits stabilization; reassociation requires K^+	9
(Na^+, K^+)-ATPase	Na^+, K^+		10
Oxaloacetate decarboxylase	Na^+		11
Phosphate acyltransferase	K^+ (NH_4^+)	*Clostridium kluyveri*	12
L-Serine dehydratase	K^+ (NH_4^+)		13
Aldehyde dehydrogenase	K^+	Tl^+ binds at K^+ sites and inhibitory sites	14
rec BC enzymes	K^+	*E. coli*	15
Tryptophanase	K^+ (NH_4^+)	*E. coli*; Na^+ inactive	16
Tryptophan synthetase	K^+ (NH_4^+)	*E. coli*	17
		Bacillus subtilis	18
Serine dehydrase	K^+	Liver	19
		E. coli	20
Glycerol dehydrase	K^+		21
Ethanolamine deaminase	K^+		22
Propanediol dehydrase	K^+ (NH_4^+, Rb^+)	Na^+, Cs^+ half as effective	23
Fructose-1,6-bisphosphatase	K^+, Na^+	Cation dependence varies with temperature	24
DNA polymerases	K^+ (NH_4^+)	High concentrations lead to inhibition	25, 26
DNA polymerase (herpes virus)	Na^+ or K^+		27

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The mechanisms by which these cations activate enzymes are often uncertain. It appears unlikely in general that they bind substrate, and more probable that they bind to the enzyme and either stabilize a conformation, or bring about conformational change. In this case, they are probably bound some distance from the substrate and exert long range effects. In some instances dissociation of subunits of proteins is prevented by binding of these cations.

Suelter[90] has classified enzymes that are activated by monovalent cations into two groups. One involves the catalysis of phosphoryl-transfer reactions and the other a variety of elimination and/or hydrolytic reactions in which a keto–enol tautomer can be invoked as an intermediate. The M^+ cation is then required to stabilize the enolate anion. It is still not possible to verify this hypothesis, but it seems unlikely in view of the comments above.

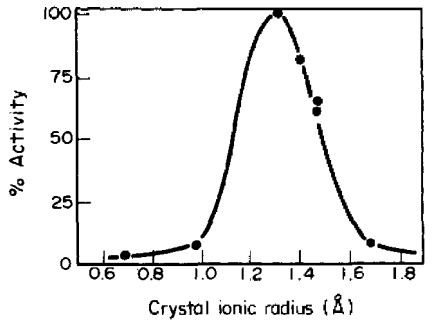


Figure 7 Activation of pyruvate kinase by monovalent cations [reproduced with permission from J. J. Villafranca and F. M. Raushel, 'NMR and EPR Investigations of Bi-Metalloenzymes' (*Adv. Inorg. Biochem.*, 1982, 4, 292), Elsevier, Amsterdam]

One of the best studied enzymes involving phosphoryl group transfer is pyruvate kinase, which catalyzes the transfer of a phosphoryl group from phosphoenolpyruvate to ADP. Pyruvate kinase requires a mono- and a di-valent cation for activation, and will be discussed in more detail in Section 62.1.3. It is well known that K^+ is the most effective monovalent activator. Figure 7 shows[94] how the activity of the enzyme varies with the ionic radius of the monovalent cation. It is clear that NH_4^+ (1.43 Å), Rb^+ (1.47 Å) and Tl^+ (1.47 Å) are able to replace K^+ (1.33 Å), while Li^+ (0.68 Å), Na^+ (0.97 Å) and Cs^+ (1.67 Å) are ineffective. Studies in which K^+ has been replaced by Tl^+ have been most informative. Tl^+ has an affinity some 50 times greater than K^+ for the potassium site, and so its binding could be detected more readily by equilibrium dialysis techniques. This showed that four Tl^+ cations were bound per molecule of enzyme, which has four subunits. The replacement of Mg^{2+} by Mn^{2+} allows distance measurements to be made from Mn^{2+} to the site of NMR active monovalent cations. As discussed later, this allows a structure of the active site in pyruvate kinase to be established[95] which shows that the phosphenolpyruvate substrate is linked to the enzyme surface through K^+ (Figure 8). The activation of pyruvate by K^+ has been used[96] as an analytical method for K^+ in the range 10^{-7} to 10^{-12} mol dm^{-3}.

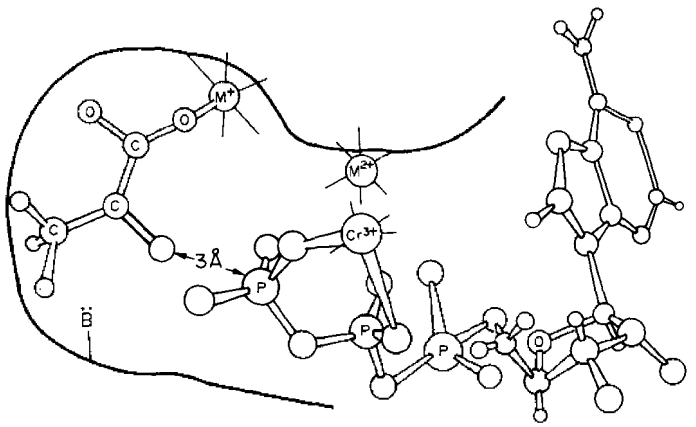


Figure 8 The active site of pyruvate kinase (reproduced with permission from *Biochemistry*, 1979, **18**, 4347, American Chemical Society, Washington, DC)

Similar studies have been carried out on the carbamoyl-phosphate synthetase from *E. coli*,[94] which requires a divalent cation plus two metal-ATP sites and a monovalent cation, as shown in equation (2).

$$2ATP + HCO_3^- + \text{glutamine} \xrightarrow{M^{2+}/M^+} 2ADP + P_i + \text{carbamoyl-P} + \text{glutamate} \qquad (2)$$

Other classes of enzyme included in Table 5 are the pyridoxal phosphate enzymes and those associated with vitamin B_{12}.

The activity of yeast aldehyde dehydrogenase is rapidly lost on removal of activating K^+. Recovery of activity on replacement of K^+ involves two conformational changes, both of which must occur to give the active enzyme. These conformational changes appear to be induced by the binding of K^+. The enzyme contains four subunits. Equilibrium dialysis shows the presence of 16 sites for Rb^+, *i.e.* four binding sites per subunit. These are sites for K^+. The cation Tl^+ also activates the enzyme at low concentration, but causes inhibition at high concentration. It appears that Tl^+ binds first at the K^+ sites with activation, and then binds at additional sites causing inhibition. This is confirmed by equilibrium dialysis experiments that show there are six sites for Tl^+ per subunit.[97]

The enzyme controlled by the *E. coli* genes recB and recC has several activities *in vivo* associated with substrate DNA, notably the degradation of single- and double-stranded DNA. Activity depends upon the presence of K^+, which is suggested to maintain the conformation of the enzyme in the active form.[98] Many DNA polymerases are stimulated as much as five-fold by cations, particularly K^+ and NH_4^+, at concentrations up to 50 mM.[99] At higher concentrations of M^+, most DNA polymerases are inhibited. Inhibition by monovalent cations has been used to distinguish between DNA polymerase-α and -β from eukaryotic cells, since the latter enzyme is not inhibited by concentrations as high as 300 mM. A DNA polymerase coded for by herpes virus is uniquely stimulated by both Na^+ and K^+. Little is known about the mechanism of action of the IA cations in these cases.

62.1.2.3.2 Alkali metal ions as structure stabilizers and other functions

The polymerization and stabilization of ribosomes are influenced by the presence of potassium and other monovalent cations in the medium, and also by Mg^{2+}. Potassium is thus essential for protein synthesis in that it controls the structural integrity of the ribosomes, but it also appears to facilitate amino acid incorporation by transfer from the RNA to the polypeptide chain in the ribosome.

The binding of alkali metals can affect the structure of DNA (although divalent cations exert stronger effects). Alkali metal cations will interact with the negatively charged phosphate group with stabilizing effects. Such interactions are often treated electrostatically without reference to specific binding sites. The DNA double helix exists in several different conformations. Thus the common form, the B form, has the base pairs arranged perpendicular to the helical axis, while the A form has the base pairs forming an acute angle with the axis. The transition of the B form to the A form can be brought about by a number of reagents, such as ethanol or guanidine, but it may be prevented by Li^+ or K^+ which stabilize the B form. The presence of excess cation has a destabilizing effect.[100]

The formation of the polynucleotide structure poly(I) is strikingly cation dependent, and relates to the size of the alkali metal cation in the central cavity. Lithium and cesium cations are too small or too large respectively to bind effectively. Na^+ occupies a site that is 2.2 Å away from four carbonyl oxygens, while K^+ is able to occupy a site 2.8 Å away from eight carbonyl oxygens.[101]

The ordering effect of alkali metal cations on nucleotides is shown by NMR studies on 5′-guanosine monophosphate. The dilithium and dicesium salts do not give a structured complex, while K_2(5′-GMP), Na_2(5′-GMP) and Rb_2(5′-GMP) all appear to have different ordered structures. The structure of the K^+ salt survives at higher temperatures showing it to be more stable.[102,103]

K^+ is also involved in carbohydrate metabolism and the uptake of phosphates in microorganisms.

62.1.3 MAGNESIUM, MANGANESE AND CALCIUM

There is an enormous literature describing the biological chemistry of these cations, particularly magnesium and calcium, the Group IIA cations. Manganese has been included in this section, as often Mn^{2+} can substitute for Mg^{2+} and enzymes may have either one of these two cations present. Manganese does play a unique role in some proteins, and these will be discussed separately. As a transition element, manganese has variable oxidation states and appears as Mn^{III} with a redox function, in superoxide dismutase, pseudocatalase and in the photosynthetic production of dioxygen by the reduction of water.

62.1.3.1 Probes for Mg^{2+} and Ca^{2+}

Much work has been carried out in which these cations have been replaced by other cations having suitable electronic or nuclear properties to allow the application of instrumental techniques to the characterization of the metal-binding site. For such substitutions to be effective, the probe metal ion should be of similar ionic radius and chemistry to the native metal ion.

The best replacement cation for Mg^{2+} on a size basis is Ni^{2+}. However, Ni^{2+}-substituted enzymes are usually inactive, with the exception of phosphoglucomutase. The failure of Ni^{2+} to activate these enzymes is usually attributed to the relative lack of lability of Ni^{II} complexes. In phosphoglucomutase the metal cation is bound to the leaving group and so the reluctance of Ni^{II} to vacate its site is of no significance.

In view of these problems with Ni^{2+}, Mn^{2+} has been used as a probe for Mg^{2+} with some success. However, it should be noted that there is a difference in radius which may be manifested in different biochemical behaviour (Mn^{2+}, 0.80 Å; Mg^{2+}, 0.65 Å). Thus Mn^{2+} has been used to probe the Mg^{2+} site in pyruvate kinase.[95] While the Mg^{2+}-activated enzyme is inhibited by Ca^{2+} and Li^{+}, the Mn^{2+}-activated enzyme is inhibited by Ca^{2+} and not by Li^{+}. There are also differences in the catalytic and regulatory properties of the NAD^{+}-specific malic enzyme of *E. coli*,[104] depending upon whether the divalent activator is Mn^{2+} or Mg^{2+}. It is necessary, therefore, to express a cautionary note. These two cations may act in slightly different ways to bring about a similar final result. In the second example it appears that the metal cofactors stabilize two different conformational states of the enzyme.

The fact that Mn^{2+} may also be used[105] as a probe for Ca^{2+} serves to emphasize those problems, as Ca^{2+} and Mg^{2+} tend to be mutually inhibitory. It appears that Mn^{2+} resembles Ca^{2+} in terms of movement in and out of certain cells. However, Mn^{2+} is taken up by some microbes through low affinity magnesium transport systems. These organisms usually have specific high affinity transport systems for Mn^{2+} as well.[106]

Lanthanides are well-known probes for calcium, although they bind to sites more strongly than Ca^{2+} and do not enter cells. One useful feature is that a series of probes of slightly differing radii may be used. Tb^{III} has a radius (1.00 Å) very close to that of calcium (0.99 Å), and has been used successfully in many instances. The Ln^{III} ions have also been used to probe sites on nucleic acids normally filled with essential Mg^{2+} ions.[107,108]

62.1.3.2 Coordination Chemistry and Biological Roles for Mg^{2+} and Ca^{2+}

The relevant chemistry of these two cations has been reviewed.[1,109-112] It is appropriate to recall their differing distribution. The concentrations of Ca^{2+} inside and outside the cell are approximately 10^{-6} and 10^{-3} mol dm^{-3} respectively, while the reverse distribution is true of Mg^{2+}. This selectivity is reflected in the chemistry of ligands that are able to distinguish between these two cations. The principles underlying the selective binding of K^{+} and Na^{+} by crown ethers, cryptands and antibiotic ionophores (Section 62.1.2.1) also apply for Mg^{2+} and Ca^{2+}. Some ionophores for Ca^{2+} are listed in Table 4. Often Na^{+} and Ca^{2+} are bound by the same ligands in view of their similar radii. However, Ca^{2+} is a better polarizer and can be distinguished against[1] by the use of ligands having hydrophobic substituents. Hydrated calcium ions are less able to lose their hydration shell and so cannot compete with Na^{+}.

Particular attention should be paid to ionophore A23187, a polyether antibiotic produced by *Streptomyces* organisms, which also synthesize a range of other polyether antibiotics. This ionophore has been used extensively in the mediation of calcium transport in a diverse range of processes. The structure of A23187 is included in Figure 5. Its absolute configuration is known.[113]

The coordination chemistry of Mg^{2+} and Ca^{2+} is dominated by oxygen-donor ligands. The geometry of their complexes tends to be different. Complexes of Mg^{2+} usually involve coordination number six with regular geometry. In contrast Ca^{2+} is able to form higher coordination number complexes with distorted stereochemistry. This difference is probably relevant to the differing biological roles of Ca^{2+} and Mg^{2+}. It explains why Ca^{2+} is used in the stabilization of cell walls and other structures, as this involves sites of distorted geometry and higher coordination numbers.

62.1.3.2.1 Binding of Ca^{2+} to proteins

The diverse range of activities found for Ca^{2+} in biology often involves the binding of Ca^{2+} to a specific calcium-binding protein. These proteins may be the first receptor sites for intracellular

calcium function, or calcium storage proteins, or calcium-dependent enzymes, or binding sites on the outer surface of plasma membranes. Many reviews are available on calcium-binding proteins and the biological function of calcium.[114–119]

The structures of some of these proteins have been determined by X-ray crystallography. Details of the binding sites for calcium are shown in Table 6. It may be seen that only oxygen donors are involved: carboxylate groups of aspartic and glutamic acids, hydroxyl groups of serine and threonine, peptide carbonyl oxygen atoms or water. Coordination numbers are often higher than six.

Table 6 Sites for Ca^{2+}

Protein		*Ligands*	*Ref.*
Thermolysin	1	Asp-138, Glu-177, Asp-185, Glu-187, Glu-190, H_2O	1
	2	Glu-177, Asp-183, Asp-185, Glu-187, Glu-190, $2H_2O$	
	3	Asp-57, Asp-59, Glu-61, $3H_2O$	
	4	Tyr-193, Thr-194, Ile-197, Asp-200, H_2O	
Trypsin		Glu-70, Glu-80, Asn-72, Val-75, $2H_2O$	2
Staphylococcus nuclease		Asp-21, Asp-40, Thr-41, $3H_2O$	3
Phospholipase A_2		Tyr-28, Gly-30, Gly-32, Asp-49, $2H_2O$	4
Parvalbumin	I	Asp-51, Asp-53, Ser-55, Phe-57, Glu-59, Glu-62 (CN = 6)	5
	II	Asp-90, Asp-92, Asp-94, Lys-96, Glu-101, H_2O (CN = 8)	
Concanavalin A		Asp-10, Tyr-12, Asx-14, Asp-19, $2H_2O$	6
Intestinal Ca BP	I	Ala-15, Glu-17, Asp-19, Glu-22, Glu-27 (bidentate), H_2O	7
	II	Asp-54, Asn-56, Asp-58, Glu-60, Glu-65 (bidentate)	
Calmodulin[a]	I	Asp-20, Asp-22, Asx-24, Thr-26, Thr-28, Glu-31	
	II	Asp-56, Asp-58, Asx-60, Thr-62, Asp-64, Glu-67	
	III	Asp-93, Asp-95, Asx-97, Tyr-99, Ser-101, Glu-104	
	IV	Asn-129, Asp-131, Asp-133, Glu-135, Asn-137, Glu-140	
Troponin C[a]	I	Asp-27, Asp-29, Asp-33, Ser-35, Glu-38, H_2O	
	II	Asp-63, Asp-65, Ser-67, Thr-69, Asp-71, Glu-74	
	III	Asp-103, Asn-105, Asp-107, Tyr-109, Asp-111, Glu-114	
	IV	Asp-139, Asn-141, Asp-143, Arg-145, Asp-147, Glu-150	
S100[a] (trigger in nerve cells)		Asp-61, Asp-63, Asp-65, Glu-67, Asp-69, Glu-72	

[a] Structures are based upon sequence analogies and NMR data.

1. B. W. Matthews, L. H. Weaver and W. R. Kester, *J. Biol. Chem.*, 1974, **249**, 8030; B. W. Matthews and L. H. Weaver, *Biochemistry*, 1974, **13**, 1719.
2. W. Bode and P. Schwager, *J. Mol. Biol.*, 1975, **98**, 693.
3. F. A. Cotton, E. E. Hazen and M. J. Legg, *Proc. Natl. Acad. Sci. USA*, 1979, **76**, 2551.
4. B. W. Dijkstra, K. H. Kalk, W. G. J. Hol and J. Drenth, *J. Mol. Biol.*, 1981, **147**, 97.
5. R. H. Kretsinger and C. E. Nockolds, *J. Biol. Chem.*, 1973, **248**, 3313; R. H. Kretsinger, *CRC Crit. Rev. Biochem.*, 1980, **8**, 119.
6. G. N. Reeke, J. W. Becker and G. M. Edelman, *J. Biol. Chem.*, 1975, **250**, 1525.
7. D. M. E. Szebenyi, S. K. Obendorf and K. Moffat, *Nature (London)*, 1981, **294**, 327.

This table does not include any examples of the 'gla' proteins. These calcium-binding proteins require vitamin K for their biosynthesis and in particular for the formation of γ-carboxyglutamate residues. In the absence of vitamin K, these residues are replaced by glutamate. The γ-carboxyglutamate group (shown in Figure 2) seems to be a particularly good binding group for calcium. An example of a 'gla' protein is prothrombin, involved in the coagulation of blood, which contains 10 γ-carboxyglutamate residues and binds 10 Ca^{2+} per molecule.[120] Several 'gla' proteins, notably those involved in blood coagulation, also have gla-independent Ca^{2+} sites of high affinity which involve the β-hydroxyaspartate residue.

62.1.3.2.2 Ca^{2+} and Mg^{2+} as structure stabilizers

Both cations play a stabilizing role in various biological structures. Calcium ions are necessary to link the 24-subunit aggregates of the dioxygen carrier hemocyanin of *Limulus polyphemus* into the native 48-subunit molecule.[121] The divalent character of Ca^{2+} probably allows it to crosslink

negative groups in the subunits. This is suggested to be the explanation of a similar dependence upon Ca^{2+} of the giant hemoglobin erythrocruorin.[122] It is noteworthy that Mg^{2+} is unable to substitute for Ca^{2+} in the stabilization of the native hemocyanin.

While Mg^{2+}, Zn^{2+} and Ca^{2+} are all found in bacterial cell walls, Ca^{2+} seems to be of particular importance in stabilization, probably because of its special ability to bridge carboxylate groups. Incubation of *Pseudomonas aeruginosa* with EDTA removes the Ca^{2+} and gives osmotically fragile species, which can be restored by addition of Ca^{2+}.

Thermolysin is a zinc endopeptidase isolated from the thermophilic organism *Bacillus thermoproteolyticus*, which can grow at high temperatures. The zinc is essential for catalytic activity, but the stability of the enzyme at high temperature with respect to denaturation results from the presence of four calcium ions per mole (Table 6). The metal-free protein shows a thermal transition at about 48 °C while the native enzyme is heat stable up to about 80 °C. The zinc-free thermolysin has similar heat stability, showing that the stabilization is due to calcium. It has been shown that calcium ions prevent the unfolding of the protein, although it is not fully understood why the stabilizing effect is so pronounced in thermolysin compared to other enzymes.[123]

Magnesium ions have a stabilizing effect on ribosomes, as noted during the discussion on potassium. In bacteria, the major portion of the intracellular Mg^{2+} and K^+ may be associated with the ribosomes. *In vitro* studies suggest that a low $[K^+]/[Mg^{2+}]$ ratio is necessary for tight crosslinks in the RNA and for ribosomal aggregation. A high ratio results in dissociation of the ribosomes into subunits and the unfolding of the RNA chain. Magnesium starvation leads to the release of ribosomal proteins from *E. coli*.[124]

Addition of Mg^{2+} stabilizes polynucleotides[100] and the DNA double helix. Denaturation of DNA is accompanied by release of Mg^{2+}. In both cases Mg^{2+} reduces the electrostatic charge associated with the phosphate groups.

62.1.3.2.3 Calcium as a regulator of cellular activities

The release of Ca^{2+} into the cell either from outside or from internal organelles can trigger off a wide range of physiological or biochemical processes. An assessment of this process requires an understanding of how Ca^{2+} enters the cell, the binding site for Ca^{2+} and subsequent activity, and how the Ca^{2+} is removed from the cytoplasm back into store. In subsequent sections, consideration will be given to transport mechanisms, binding proteins and detailed examples of trigger processes.

62.1.3.2.4 Magnesium (manganese) and calcium ions as enzyme activators

The main role of the IIA cations in the activation of enzymes seems to be that of weak Lewis acids. In addition the cation may serve as a template to bridge enzyme and substrate and bring them into the correct relative orientation for reaction. Furthermore these cations may stabilize or produce certain protein conformations. Thus glutamine synthetase binds 24 moles of Mn^{2+} per mole of protein. The binding of the first 12 cations results in conformational changes that lead to the formation of 12 new sites for the binding of the remaining 12 cations, which then have a catalytic role.

Mg^{2+} is associated with a large number of enzymes involving the hydrolysis and transfer of phosphates. The MgATP complex serves as the substrate in many cases. As noted in Section 62.1.2.2.2, the interaction of Mg^{2+} with the ATP enhances the transfer (to a substrate or water) of the terminal phosphoryl group. The results of many studies with model compounds lead to the postulate of an S_N2 mechanism for this reaction.[125] Associative pathways allow greater control of the stereochemistry of the substitution, and the rates of such processes are accelerated more effectively by metal ions.

62.1.3.3 Transport of the IIA Cations

The best studied example of a Group IIA cation transport system is the calcium pump of the sarcoplasmic reticulum of skeletal muscle. Indeed, the calcium pump and the sodium pump represent the most studied of all transport processes. The calcium pump involves a membrane-bound (Ca^{2+}, Mg^{2+})-ATPase and uptake of Ca^{2+} is associated with hydrolysis of ATP. While the

calcium pump does not involve counter transport of Mg^{2+}, there are notable similarities with the sodium pump. Both involve an intermediate phosphoprotein, there is similar primary structure around the active site of phosphorylation, and conformational changes have been detected in certain parts of the reaction cycle. A range of other calcium transport processes and microbial systems for Mg^{2+}, Ca^{2+} and Mn^{2+} are known.

62.1.3.3.1 The (Ca^{2+}, Mg^{2+})-ATPase of sarcoplasmic reticulum

The sarcoplasmic reticulum (SR) is a specialized membraneous network surrounding the myofibrils of skeletal muscle that regulates the concentration-relaxation cycle of the muscle by releasing and reaccumulating Ca^{2+}. Muscle contracts when myoplasmic [Ca^{2+}] reaches 10^{-6} mol dm^{-3} and relaxes as Ca^{2+} is pumped back into the SR. Release of Ca^{2+} is triggered by an action potential at the neuromuscular junction, and occurs by processes yet to be clarified. The released Ca^{2+} binds at sites on muscle fibres and triggers contraction. Immediately the Ca^{2+} is taken up again into the SR by the membrane (Ca^{2+}, Mg^{2+})-ATPase, and stored on calcium-binding proteins, notably calsequestrin, which bind large amounts of Ca^{2+} with high affinity.

Various aspects of the (Ca^{2+}, Mg^{2+})-ATPase have been reviewed.[126-135] It can be isolated in vesicular form from homogenized skeletal muscle. Since it is the major protein component of SR membranes, it can also be isolated fairly easily in relatively pure form. The enzyme has a molecular weight in the range 100 000–120 000, and forms oligomers in the SR membranes, probably tetramers.[133] Each subunit is associated with about 30 molecules of phospholipid, which are suggested to form a shell or annulus around the protein. The monomeric subunit has ATPase activity, and remains monomeric throughout the enzyme cycle,[136] although the behaviour of the monomer is dependent on the solubilization procedure.[137]

Activity is modulated by other proteins present in the membrane. These include a glycoprotein (MW 53 000) which stimulates ATPase activity;[138] a 60 000 molecular weight protein, which is phosphorylated in a calmodulin-dependent fashion, affects accumulation of calcium;[139] while the activity of the enzyme is affected by an endogenous kinase and phosphatase which phosphorylates and dephosphorylates the protein.[140] Phospholamban is a proteolipid (MW 22 000) in cardiac SR which undergoes both cyclic AMP-dependent and calcium-calmodulin-dependent phosphorylation,[141] but at different sites. All these proteins are probably involved in regulating the activity of the calcium pump.

There is much evidence, usually based upon ESR studies with spin labels, for conformational changes in the protein during the enzyme cycle. Enzyme activity shows a discontinuity in the Arrhenius plot, once attributed to phase transitions in the membrane phospholipid, but which is similar to discontinuities in the Arrhenius plot for rotational mobility and which have been rationalized in terms of a conformational change in the ATPase.[142]

Trypsin hydrolysis of SR vesicles cleaves the (Ca^2, Mg^{2+})-ATPase into three fragments, NH_2-20 000, 30 000 and 45 000-COOH. The phosphorylation site is associated with an aspartic acid residue in the 30 000 fragment and ionophoric activity with the 20 000 fragment. The amino terminus of the enzyme is located on the cytoplasmic side of the membrane.[143]

The ATPase has an absolute requirement for Mg^{2+} which is essential for the breakdown of the phosphorylated intermediate. There is evidence for at least three forms of the phosphoenzyme, only the last of which is sensitive to Mg^{2+}.[144] Monovalent cations are effective as activators in the sequence $K^+ \approx Tl^+ > Na^+ > NH_4^+ > Rb^+ \approx Cs^+ > Li^+$, again through the promotion of the loss of phosphate from the phosphorylated intermediate.[145] It has been postulated that K^+ may be involved in antiport with Ca^{2+} to maintain charge balance, but it is currently thought that this involves protons or a flux of anions.

Two moles of Ca^{2+} appear to bind to the protein per phosphorylation site. Binding of one Ca^{2+} causes a conformational change followed by binding of Ca^{2+} to a second site. The use of Ca^{2+} electrodes or arsenazo III indicator shows the ratio $Ca^{2+}/ATP = 1.82 \pm 0.13$ in the presence of saturating Ca^{2+}. The ratio decreased with increasing pH (with an apparent $pK = 7.9$), and at temperatures over 30 °C. It was also dependent upon Ca^{2+}. Thus the stoichiometry appears to vary with the physiological conditions due to 'pump slippage'.[146]

Most mechanisms for the (Ca^{2+}, Mg^{2+})-ATPase are modifications of the proposal of deMeis *et al.*[128] An example is shown in Figure 9. The ATPase can utilize CaATP and MgATP as substrates.[147] Two moles of Ca^{2+} are bound per mole of the phosphorylation site with high affinity, followed by phosphorylation of the enzyme by ATP. Conformational changes in the phosphoprotein lead to the calcium sites being accessible to the intravesicular space, with decrease in their affinity for

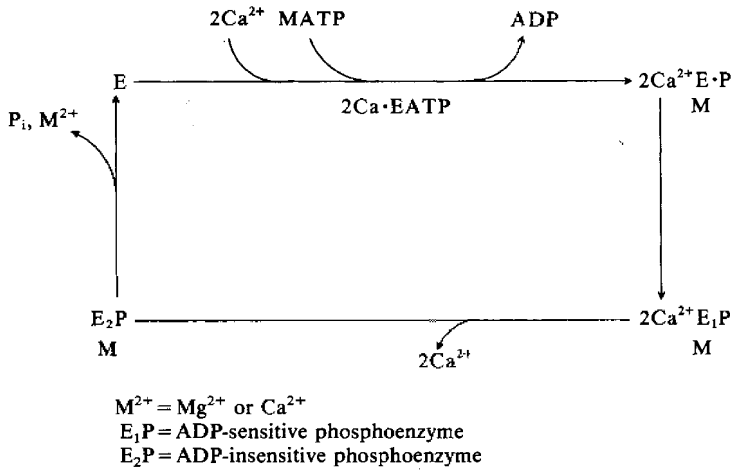


Figure 9 Schematic representation of the (Ca^{2+}, Mg^{2+})-ATPase

Ca^{2+}.[148] Calcium is released after conformational transition of the phosphoenzyme from E_1P (the ADP-sensitive phosphoenzyme) to E_2P (the ADP-insensitive phosphoenzyme).[149]

An important contribution has been made by Pickart and Jencks,[150] who have set up a thermodynamic cycle for catalysis of calcium transport based upon equilibrium constants for individual steps determined under a single set of experimental conditions. This cycle provides the necessary information to allow the evaluation of the way in which the binding energies associated with particular stages allow rapid turnover of the system under physiological conditions.

Binding sites for Ca^{2+} and ATP have been explored by the use of metal probes and nucleotide analogues. The Mn^{2+} ion substitutes for Mg^{2+} but also binds at the Ca^{2+} sites. Such complications have led to the use of lanthanides[134] as probes for the Ca^{2+} sites. Thus Gd^{3+} and Tb^{3+} compete with Ca^{2+} for the high affinity site. Luminescence studies with laser-excited Tb^{3+} at the Ca^{2+} sites show that two water molecules are present in the first coordination shell.[151] Earlier work[134] with Gd^{3+} shows that the Ca^{2+} sites are a maximum of 16.1 Å apart, and that both sites involve a low level of hydration, consistent with a hydrophobic site. Gd^{3+} has also been used as an ESR probe, and, under certain conditions, evidence has been produced for two forms of an E-Gd^{3+} complex, in accord with current mechanistic views.

Several classes of nucleotide analogue have been used recently: (1) thiophosphate derivatives of ATP; (2) ^{17}O and ^{18}O derivatives of ATP; (3) Cr^{III} or Co^{III} complexes of ATP; (4) the fluorescent analogue 2,3-*O*-(2,4,6-trinitrocyclohexyldienylidine)adenosine diphosphate;[152] and (5) photoaffinity analogues.[153]

Vanadate inhibits hydrolysis of ATP by (Ca^{2+}, Mg^{2+})-ATPase. As in the case of the (Na^+, K^+)-ATPase, it is thought that vanadate inhibits by binding at the active site and mimicking the trigonal bipyramidal transition state of an S_N2 reaction. Occupancy of the phosphate site by vanadate inhibits the binding of Ca^{2+} at the high affinity sites, even as binding of Ca^{2+} inhibits the binding of P_i. This demonstrates the interdependence of the Ca^{2+} and vanadate/phosphate sites.[154]

Efflux of calcium from the SR is very rapid, the concentration of Ca^{2+} in the sarcoplasm rising 100-fold in milliseconds. This is too fast to be accounted for by a simple reversal of the calcium pump. It has been postulated that rapid efflux occurs through hydrophilic channels in the SR membrane formed by aggregation of the (Ca^{2+}, Mg^{2+})-ATPase. As noted earlier, the enzyme exists as oligomers in the membrane. Thus the enzyme is postulated to act as a pump in one direction and as a rapid efflux channel in the other. While this idea is speculative, there is some evidence for passive permeability mechanisms for calcium in SR. Thus, in SR vesicles, accumulated Ca^{2+} can be released[155] by caffeine, ATP, increased external Ca^{2+}, low Mg^{2+}, alteration in pH or alteration in the ionic environment that could result in changes of surface membrane charge or a depolarized membrane. In addition it appears that a certain proportion of SR vesicles have enhanced 'calcium-release' properties.[156,157] It is generally thought that physiological release of Ca^{2+} from SR is induced by Ca^{2+}, depolarization of the SR membrane, changes in surface charge and/or a pH gradient.

62.1.3.3.2 Miscellaneous mammalian transport systems for Ca^{2+}

A variety of other calcium transport systems are associated with Ca^{2+}-activated ATPases. The extraembryonic structure, the chorioallantoic membrane, of the chick embryo is responsible for the translocation of over 120 mg of eggshell calcium into the embryo during development. The enzyme responsible for this is a (Ca^{2+}, Mg^{2+})-ATPase with K_m values for Ca^{2+} of 30 μmol dm^{-3} and 0.3 mmol dm^{-3}, and a molecular weight of 170 000. The enzyme can be crosslinked and co-isolated with a calcium-binding protein.[158] Transport of Ca^{2+} is also associated with (Ca^{2+}, Mg^{2+})-ATPases in neutrophil plasma membranes,[159] transverse tubule membranes from rabbit skeletal muscle,[160] rabbit myocardial membrane,[161] endoplasmic reticulum,[162] sarcolemma,[163] brain microsomes,[164] the Golgi apparatus[165] and rat liver plasma membranes.[166]

The Ca^{2+}-pumping ATPase of the red cell membrane differs from the SR calcium pump. It involves a phosphoprotein intermediate, but is a larger protein (MW ≈ 140 000) and requires activation by a Ca^{2+}–calmodulin complex in the cytosol. It is probable that similar calcium pumps exist in other plasma membranes including some described above. It seems sensible that Ca^{2+}-calmodulin complexes that mediate intracellular responses to changes in the cytosol calcium concentration should also control activation of the calcium pump that expels excess calcium from the cell. The calcium pump of the red cell membrane appears to resemble other ion pumps, having a site for the hydrolysis of ATP and a site for the binding and translocation of calcium all on one protein. However, there must be some additional feature that results in inhibition, so that it is only active when binding the Ca^{2+}–calmodulin complex. A hint comes from the observation that isolated red cell membranes, which usually require calmodulin for activity of the calcium pump, show full activity after gentle hydrolysis with trypsin. This implies that the trypsin hydrolysis has resulted in the loss of a peptide fragment which is responsible for the inhibition and which also contains the receptor site for the calmodulin.[167,168] The properties of the fragments produced on controlled hydrolysis of the ATPase with trypsin have been examined, and it appears that the fragment postulated to contain the calmodulin binding site does not bind calmodulin after it is split from the main molecule.[169] This does not invalidate the hypothesis but more work needs to be done.

Calcium may also be taken up by Na^+-Ca^{2+} exchange. Thus sperm plasma membranes take up Ca^{2+} by an ATP-independent Na^+/Ca^{2+} antiporter. Ejaculated sperm cannot do this, due to the presence of a protein that binds strongly to the plasma membrane.[170] A highly active, electrogenic Na^+/Ca^{2+} exchange occurs in sarcolemmal vesicles from cardiac muscle.[171]

62.1.3.3.3 Calcium transport in mitochondria

Calcium levels are believed to be controlled in part at least by the uptake and release of Ca^{2+} from mitochondria.[172–174] The capacity of mitochondria for Ca^{2+} seems to be more than sufficient to allow the buffering of Ca^{2+} at low cytosol levels. Mitochondria take up Ca^{2+} by an energy-dependent process either by respiration or ATP hydrolysis. It is now agreed that Ca^{2+} enters in response to the negative-inside membrane potential developed across the inner membrane of the mitochondrion during respiration. The uptake of Ca^{2+} is compensated for by extrusion of two H^+ from the matrix, and is mediated by a transport protein. Previous suggestions for a Ca^{2+}-phosphate symport are now discounted. The possible alkalization of the mitochondrial matrix is normally prevented by the influx of H^+ coupled to the influx of phosphate on the H^+-$H_2PO_4^-$ symporter (Figure 10). This explains why uptake of Ca^{2+} is stimulated by phosphate. Other cations can also be taken up by the same mechanism.

If respiration is inhibited, mitochondria can still take up Ca^{2+} as long as ATP is available, since hydrolysis of ATP can also generate a transmembrane potential.

The presence of phosphate increases the ability of the mitochondria to accumulate Ca^{2+}, partly because of the buffering effect of the phosphate on the pH of the matrix, and partly because of the precipitation of insoluble calcium phosphate within the matrix. The formation of insoluble calcium phosphate lowers the internal free [Ca^{2+}] and favours further influx. The amorphous nature of the precipitate is of interest as the formation of crystalline hydroxyapatite would be expected. Mitochondria must contain a factor that inhibits this process.

The proteins that are responsible for mitochondrial Ca^{2+} uptake have not been identified with certainty. Various glycoproteins isolated from mitochondria are probably Ca^{2+} receptor proteins rather than Ca^{2+} transporters. However, a 3000 molecular weight Ca^{2+}-binding protein has been isolated from the inner membrane of calf heart mitochondria which has properties appropriate

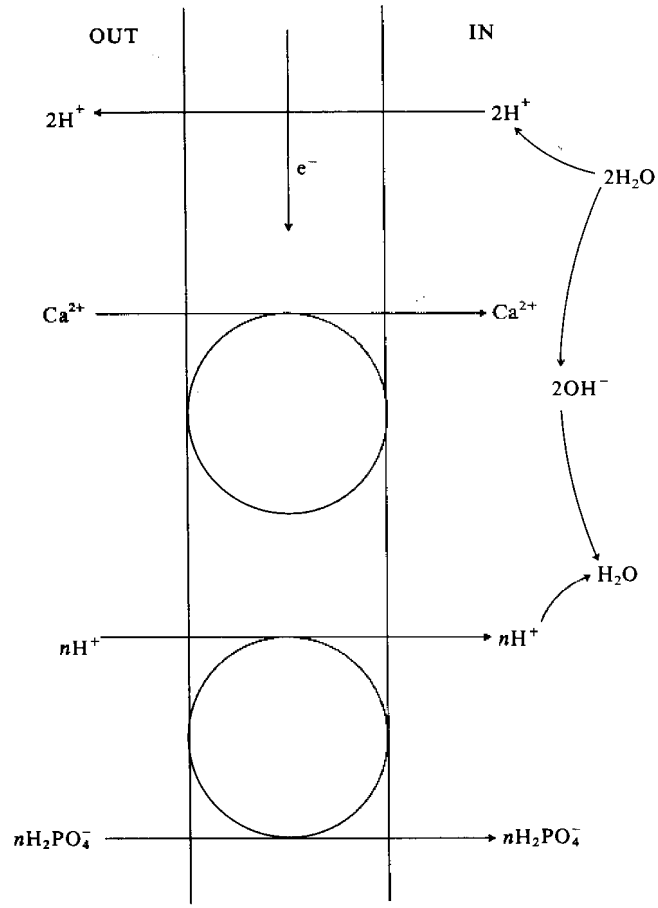


Figure 10 Respiration-dependent uptake of Ca^{2+} by mitochondria

for the Ca^{2+} carrier. This protein, calciphorin, carries Ca^{2+} through an organic phase, and is inhibited by La^{3+} and by ruthenium red, the classical inhibitors of calcium uptake in mitochondria.[175]

Efflux of calcium from mitochondria is less well understood. It can be induced by uncouplers or by inhibition of electron transport, which results in the reversal of the Ca^{2+} uptake porter as Ca^{2+} efflux runs down the Ca^{2+} concentration gradient. However, there are additional pathways, possibly *via* a Ca^{2+}–$2H^+$ antiport carrier. A chemically diverse range of compounds act as Ca^{2+}-releasing agents, while some intracellular regulatory factors may be physiological regulators (*e.g.* cAMP, Na^+, pyrophosphate, phosphoenolpyruvate, redox state of pyridine nucleotides).[172] It is possible that these agents act indirectly by affecting the mitochondrial permeability to other substances, for example by the activation of hydrophilic channels in the inner membrane. Calcium can produce a reversible increase in permeability of the mitochondrial inner membrane (the Ca^{2+}-induced membrane transition). The rate of induction of this transition is also dependent on a number of factors listed above. It should be noted that Ca^{2+} efflux differs in mitochondria isolated from various sources.

62.1.3.3.4 Transport of the IIA cations in microbes. Sporulation

Some illustrative examples of transport of Mg^{2+}, Mn^{2+} and Ca^{2+} in microbes will be given in this section, and particular attention paid to cation uptake during sporulation. A number of transport processes will be described, which illustrate well the value of cation-selective ionophores in the study of cellular physiology. Excellent reviews of earlier work are available.[177-180]

In view of the substantial requirement of bacteria for Mg^{2+}, it is not surprising that selective, active transport processes are available for its uptake.[178] The bacterium *E. coli* has two kinetically

distinct transport systems for Mg^{2+}, as shown by studies with mutants defective or altered in these transport systems.[181] The first, system I, has high affinity for Mg^{2+}, with $K_m = 30\ \mu mol\ dm^{-3}$. It also takes up Mn^{2+}, Ni^{2+} and Co^{2+} with lowered activity, although it should be stressed that these cations may well have separate transport processes of high affinity for uptake at lower concentrations. The second, system II, also has a K_m value of about 30 $\mu mol\ dm^{-3}$, and is probably specific for Mg^{2+}. It is repressed by growth in media of high magnesium concentration. Some bacteria require citrate as a charge-compensating cotransported anion.

The uptake of Mn^{2+} or Co^{2+} by system I is inhibitory or lethal respectively, and leads to efflux of Mg^{2+} from the cell. It is likely that accumulated Mn^{2+} or Co^{2+} displaces Mg^{2+} from ribosomes, thus increasing intracellular 'free' magnesium ions, which leave the cell *via* the Mg^{2+} transport systems.

Both systems for Mg^{2+} uptake are temperature dependent and are inhibited by uncouplers and respiratory chain inhibitors, showing them to be active processes.

Energy-dependent transport systems of high affinity for magnesium have also been identified in fungi and yeasts. Mg^{2+} moderates the mutagenic and growth-inhibiting actions of Mn^{2+} on *Saccharomyces cerevisiae*, probably by competing for the same uptake system. Energy-dependent uptake of Mg^{2+} in this case requires phosphate for cotransport. In eukaryotic cells there are sometimes compartmentalized deposits of magnesium phosphate.

Highly specific, active transport systems for manganese have been found for a wide range of organisms.[179] Their high affinity for Mn^{2+} allows organisms to concentrate Mn^{2+}, even in the presence of much higher levels of calcium and magnesium. Thus the *E. coli* manganese transport system has a K_m value of 0.2 $\mu mol\ dm^{-3}$ and is unaffected by a 10^5-fold excess of Mg^{2+} or Ca^{2+}. Both Co^{2+} and Fe^{n+} appear to compete for the Mn^{2+}-uptake system, but their K_i values are over 100 times greater than the K_m value for Mn^{2+}. The system is effectively specific for Mn^{2+}. In addition, at higher concentrations, cells can acquire Mn^{2+} because it is a low affinity substrate for the Mg^{2+} transport system. *Bacillus subtilis* has a citrate-Mn^{2+} cotransport system, while yeasts have a phosphate-Mn^{2+} system, as observed for Mg^{2+}.

Certain marine bacteria take up Mn^{2+} and oxidize it to Mn^{IV}, which is precipitated as MnO_2. These processes are thought to be involved in the formation of ferromanganese nodules, which may contain up to 63% of their weight as MnO_2.[179] Relatively little is known about the mechanism of formation of these nodules, but their potential as a reserve of manganese (and other metals) is enormous. A recent suggestion is that the oxidation of Mn^{2+} is carried out by the spores of a marine *Bacillus* rather than the cells. Oxidation of Mn^{2+} did not occur in the absence of binding of Mn^{2+} to the spores. Oxidation and deposition of manganese only took place after Mn^{2+} was bound to the spore.[182,183]

B. subtilis has a highly specific requirement (1 $\mu mol\ dm^{-3}$) for Mn^{2+} for sporulation. No alternative cation can replace Mn^{2+}, although other cations are also required. Uptake of Mn^{2+} by *B. subtilis* is an active, highly specific process, similar to that described for *E. coli*. Thus, uptake of Mn^{2+} is unaffected by a 10^5-fold molar excess of Mg^{2+} or Ca^{2+}, but has a K_m value of about 1 $\mu mol\ dm^{-3}$. The manganese accumulated by non-sporulating cells is exchangeable with extracellular Mn^{2+}. In sporulating cells this was not the case, and after 9 h into sporulation 100% of the Mn^{2+} from media containing low levels of Mn^{2+} was found in the mature spores. Mn^{2+} is essential for the synthesis of certain antibiotics by *Bacillus*, including gramicidin A, bacitracin and mycobacillin.[179] These were once thought to be involved in the transport of Mn^{2+} during sporulation, but these ideas are now discounted. The role of cations in sporulation will be discussed at the end of this section.

Microbial cells maintain low internal $[Ca^{2+}]$ levels through the operation of several types of highly active and specific efflux processes.[180,184] Efflux of Ca^{2+} can only be studied with difficulty in whole cells, partly because of complications resulting from the binding of Ca^{2+} to the cell walls. Nevertheless, the presence of active mechanisms for the efflux of calcium are shown by the fact that extreme temperatures or inhibitors result in increased levels of intracellular calcium. Efflux of Ca^{2+} has been demonstrated for *B. megaterium*, while ATP-linked efflux of Ca^{2+} has been demonstrated for *Streptococcus faecalis*.[185]

Most results on calcium transport have been obtained using cytoplasmic membrane vesicles, which may be prepared in 'inside-out' or 'right-side-out' configurations. Inside-out vesicles may be obtained by the disruption of *E. coli* cells in a French press. These then accumulate Ca^{2+} in an energy-dependent fashion, provided ATP or an oxidizable substrate is available. Addition of phosphate enhances the uptake of calcium as calcium phosphate is precipitated inside the cell, thus accounting for the lack of exchangeability of the calcium.[186]

The calcium uptake process appears to involve exchange with H^+. Thus the ionophore nigericin, which catalyzes an H^+/K^+ exchange, inhibits uptake of calcium in the presence of potassium.

This results in the loss of the H^+ gradient. The ionophore A23187 stimulates calcium uptake. The Ca^{2+}/H^+ ratio appears to be electrogenic, but published values of the ratio are 1:1[187] or 1:>2.[188] These ion movements are shown schematically in Figure 11. It should be noted that the orientation of the protonmotive force is reversed from that *in vivo*. The proton-pumping Mg^{2+}-ATPase will be described in a later section. This calcium transport system is not inhibited significantly by ruthenium red, the classical inhibitor for calcium uptake in mitochondria. However, uptake of Ca^{2+} by these inside-out vesicles of *E. coli* is inhibited dramatically[189] by a dimeric, mixed-valence complex of $Ru^{II,III}$, $[(NH_3)_3RuCl_3Ru(NH_3)_3]^{2+}$. The mode of action remains to be established.

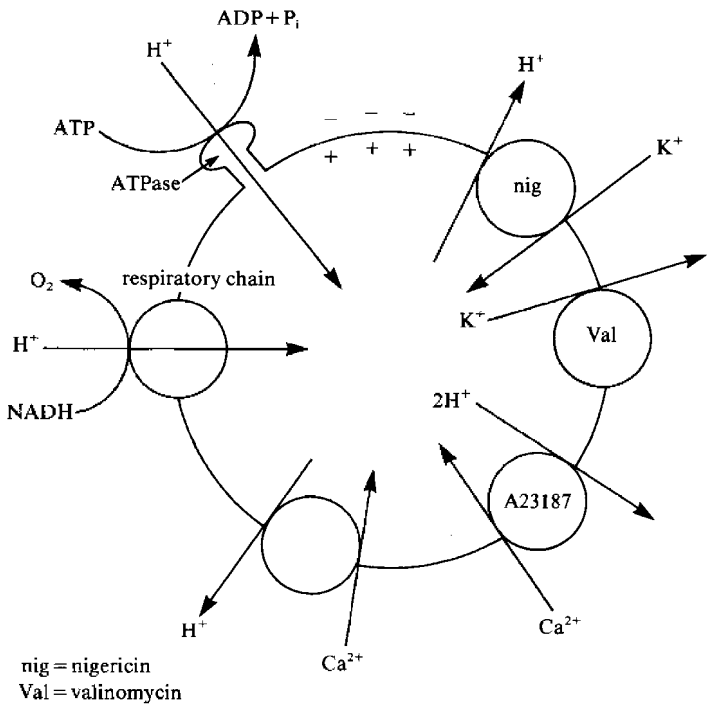


Figure 11 Uptake of Ca^{2+} by inside-out membrane vesicles of *Escherichia coli*

Recently, a second transport system for efflux of Ca^{2+} from *E. coli* has been identified.[190] This is a calcium–phosphate symporter, which catalyzes a 1:1 cotransport of calcium and phosphate, probably in exchange for protons.

Active transport of Ca^{2+} across the plasma membrane of *Neurospora crassa* involves a Ca^{2+}/H^+ exchange,[191] although in *Halobacterium halobium* movement of Ca^{2+} is linked to Na^+.[192] The primary gradient generated is a proton gradient, but an H^+/Na^+ antiporter develops an Na^+ gradient which is used to extrude Ca^{2+}. Efflux of Ca^{2+} is not inhibited by proton-conducting uncouplers but is sensitive to monensin, an ionophore that catalyzes an H^+/Na^+ exchange.

Thus, at least four different mechanisms have been established for the exclusion of Ca^{2+} by bacterial cells, namely, active efflux of Ca^{2+} *via* the Ca^{2+}/H^+ antiport (*E. coli*, *Azotobacter vinelandii* and *Mycobacterium phlei*), the Ca^{2+}/Na^+ antiport (*H. halobium*), *via* the hydrolysis of ATP (*S. faecalis*), and calcium–phosphate symport (*E. coli*).

Massive amounts of Ca^{2+}, up to 4% dry weight, are accumulated during sporulation in members of the genus *Bacillus*. Other divalent cations, Mn^{2+} and Zn^{2+}, are also accumulated. The Ca^{2+} is found associated with dipicolinic acid (pyridine-2,6-dicarboxylic acid). In general, bacterial spores show remarkable physiological properties, including a resistance to heat and a wide range of deleterious agents. They have no detectable metabolism when dormant but are able to germinate within minutes in response to agents such as L-alanine, heat and manganese. It is speculated that the calcium dipicolinate complex confers heat resistance to bacterial spores and helps to maintain dormancy. However, certain mutants which have normal heat resistance do not contain dipicolinic acid.[193] The precipitation of calcium dipicolinate in the spore could contribute to the passive uptake of calcium.

The uptake of Ca^{2+} by sporulating cells is of interest as it involves the reversal of the normal distribution of calcium between the intracellular compartment and the external medium. It is not

known whether the uptake of Ca^{2+} involves a reversal of the normal calcium extrusion system or whether it is an independent transport pathway. Calcium must first be translocated across the membrane of the mother cell, and then be accumulated by the forespore. The outer membrane of the forespore arises from invagination of the mother cell membrane, and therefore has inside-out orientation. It will be able to accumulate Ca^{2+} into the forespore. However, the inner membrane of the forespore will have normal orientation.

Transport into the mother cell probably involves a Ca^{2+}/H^+ antiport working in the reverse direction from normal, to give a concentration of Ca^{2+} in the range 3–9 mmol dm^{-3} in the mother cell cytoplasm. Transport into the forespore can then follow the concentration gradient, being facilitated by the precipitation of the calcium in the forespore as the dipicolinate. Added dipicolinate does not stimulate Ca^{2+} uptake into isolated forespores.[194]

The distribution of the cations in the spores has been investigated by the use of high resolution electron probe microanalysis for spores from *B. megaterium*[195] and *B. cereus*.[196] This shows that nearly all the Ca^{2+}, Mg^{2+} and Mn^{2+} is concentrated in the core region, while there is a high concentration of silicon in the cortex/coat layer. ESR spectra[197] shows the Mn^{2+} signal in the former case to be virtually identical at 77 and 298 K, suggesting it is present in a crystalline lattice. Such a lattice would be present in a Ca^{2+}/Mn^{2+} complex of dipicolinic acid.

Dormancy of the spore has been attributed[198] to the inactivation of phosphoglycerate phosphomutase by binding of Mn^{2+}. Triggering of germination is brought about by several agents. The first event detected in the triggering of *B. megaterium* spore germination is the release of Zn^{2+}. This may be liberated from a regulatory site on a protein.[199] Some 25% of the total spore Zn^{2+} pool is released from non-heat-activated spores within four minutes of triggering germination. It appears that the sequence of events overall[200] is Zn^{2+} release, commitment, cortex hydrolysis, pyridine-2,6-dicarboxylic acid and Ca^{2+} release and the onset of metabolism.

Electron probe microanalysis also shows that Ca^{2+} is a prominent constituent of the γ-particle in the zoospore of the fungus *Blastocladiella emersonii*.[201] Ca^{2+} also induced zoospores of the fungus *Phytophthora cinnamomi* to encyst, and subsequently to germinate, while other cations induced encystment only.[202] There is a high Ca^{2+} content in *Streptomyces* spores, and release of Ca^{2+} is an early event in spore germination.[203]

62.1.3.3.5 Transport of the IIA cations in plants

Most studies in this area have emphasized nutritional aspects, and the effects of nutritional deficiencies. A range of studies on uptake of Mn^{2+} by plant tissues show evidence for active transport systems.[204,205] The enzymes of photosystem II have an absolute requirement for Mn^{2+}, as does the NAD-dependent malic enzyme found in the mitochondria of certain plants. Some Mn^{2+}-containing proteins have been suggested to be involved in transport and storage of manganese. Manganin is a peanut seed globulin that contains one Mn^{2+} per protein molecule,[206] while jack bean concanavalin A also contains manganese.

Most growth and developmental processes in plants are associated with movements of calcium.[207] Calcium enters the plant through the root, mainly at the tip of the root. Large, mainly immobile concentrations of Ca^{2+} are found in the apoplastic compartment, but the cytosolic concentration of Ca^{2+} is low, and is similar to that found in animal cells. In general it appears that entry of Ca^{2+} into plant cells is passive, although its efflux is driven by active transport mechanisms. There is much evidence that the low levels of Ca^{2+} are controlled by plasma membrane Ca^{2+}-translocating ATPases and by Ca^{2+} uptake into mitochondria, vacuoles and possibly other organelles. Uptake of Ca^{2+} by plant mitochondria also involves Ca^{2+}-translocating ATPases, and appears to be similar to that found for animal mitochondria. It is stimulated by phosphate and inhibited by ruthenium red and lanthanide ions.[208] Isolated plant mitochondria contain large amounts of calcium, up to 700 nmol mg^{-1} mitochondrial protein.

Some microsomal plant membranes have Ca^{2+}-translocating ATPases which are modulated by calmodulin, as described in Section 62.1.3.3.2 for animal cells.

62.1.3.4 Calcium-binding Proteins

A wide range of calcium-binding proteins have been isolated from intracellular and extracellular sources.[115–119,209,210] They are involved in the storage of calcium, the buffering of calcium concentrations and the triggering of a wide range of processes involving membrane transport, secretion

and enzyme action, and so are associated, for example, with nerve and muscle function. Structural data for some calcium-binding proteins were included in Table 6, while Table 7 presents a more comprehensive list. These proteins have high binding constants for calcium (10^6–10^7) and much lower constants for magnesium (about 10^3), and show sequence homology in certain cases. There are variations in the calcium-binding sites in accord with the different functions of the proteins. They also bind Ca^{2+} at rates close to the diffusion-controlled limit. The trigger proteins have four sites for Ca^{2+}, which occur as two pairs of 'hands'. Other proteins have two linked sites, *i.e.* one pair of hands. These highly structural sites[211] are not seen in the calcium-storage proteins.

Table 7 Some Calcium Proteins

Protein	*Function*
Prothrombin	Extracellular trigger
Calmodulin	Intracellular trigger of enzymes and pumps
Troponin C	Trigger of contractile systems
Myosin light chains	Trigger in some muscle cells
S100	Trigger in nerve cells
Calcineurin	Phosphoprotein phosphatase
Intestinal CaBP	Calcium transport
Parvalbumin	Calcium buffer
Calsequestrin	Intracellular store
Calelectrin	Promotion of membrane aggregation
Bone proteins	Limits crystal growth (Gla proteins)
Saliva proteins	Protection of teeth (proline rich)
Statherin	

Many of these proteins, notably those involved in trigger functions, undergo substantial conformational changes on binding calcium. In this way the presence of Ca^{2+} can be used to transmit information to enzyme sites to be activated in the cell. The use of the trigger protein to interact with the enzyme allows this information to be transmitted in a more controlled way than would be the case if Ca^{2+} had interacted directly with the enzyme. The use of triggered conformational changes to control reactivity is known in biology, and is illustrated well by the cooperative effect in the dioxygen carrier hemoglobin.

In order to understand these effects in a detailed way for the calcium-binding proteins, it is necessary to compare the structure of the calcium-free and calcium-bound forms of each protein. The structures of parvalbumin and the intestinal calcium-binding protein (Wasserman protein) are known (see Table 6), but at present there are no crystal structures available for calcium-free proteins. Some structural information has been deduced from changes in the NMR spectrum as calcium is removed from the calcium-bound proteins.[209,210]

In the light of the available crystallographic studies, the amino acid sequences and NMR studies, certain general points have been noted[209] for parvalbumin, Wasserman protein, calmodulin, troponin C and S100. (1) Each calcium site is formed from residues in a hand which includes a β-strand. The sites contain backbone carbonyl and side-chain carboxylate. (2) Each binding site is linked to two helices. (3) Each β-strand backs on to another strand to form a Ca-β-sheet-Ca unit, which then involves four helices. (4) The helices interact with each other through largely hydrophobic surfaces. (5) The connections between remote ends of helices are relatively mobile strands, and differ from protein to protein. (6) The four-hand proteins, the calmodulins and troponins, are similar to the sum of their two-handed fragments.

Removal of calcium leaves most of the secondary structure unchanged and results in a small change in the twist of the β-sheet, with associated changes in the relative positions of the four helices and the exposure of new surface residues, together with differences in the link regions between helices. Loss of calcium gives a mobile, less well-structured protein, that is continually affected by change in temperature, and melts at low temperature.

Binding of calcium in the trigger reaction results in an adjustment of the β-sheet, which is transmitted *via* rotation of the helices (with the exposure of new hydrophobic residues) to the link region of the protein, which undergoes major conformational change and then binds to the enzymes to be activated. The inhibitor trifluoperazine[212] functions by binding to the surface of the helices, so hindering the trigger movement. The extent to which these hydrophobic and charged

domains are exposed may well explain the selective affinity of bovine brain calmodulin for brain phosphodiesterase, troponin C for troponin I, and *Tetrahymena* calmodulin for guanylate cyclase.

Several examples of calcium-binding proteins are discussed in the following sections. Some will be discussed further in later sections.

62.1.3.4.1 Calmodulin (CaM)

This widespread protein, of molecular weight about 17 000, regulates the activity of a number of calcium-dependent enzymes.[119,213-216] Calmodulin binds four Ca^{2+}, apparently with the induction of sequential conformational changes, as shown by studies involving NMR,[217,218] fluorescence,[219,220] CD[221,222] and Raman spectroscopy.[223] The Raman studies confirmed that the calcium-induced conformational changes involved the α-helix and β-sheet, while the UV-CD work[222] showed that the main structural event occurring in the step $CaM{\cdot}Ca_2 \rightarrow CaM{\cdot}Ca_3$ involves a gain in the α-helical content in the 83-92 sequence to expose a hydrophobic region which would interact with a target enzyme.[224] It is probable that only $CaM{\cdot}Ca_3$ and $CaM{\cdot}Ca_4$ interact with targets.

There is some uncertainty about whether or not the four sites for calcium are filled sequentially. There seems to be evidence from ^{43}Ca NMR for two high affinity sites (constants: 4×10^6 dm^3 mol^{-1}) and two low affinity sites (constants: 9×10^4 dm^3 mol^{-1}),[226] a view supported by ^{113}Cd NMR.[227] These results were obtained from solutions of low ionic strength. Other data[222] suggest that calmodulin has four nearly identical intrinsic binding constants. It may be that the binding of Ca^{2+} depends upon the presence of counter ions to shield charged groups on the protein. Terbium(III) has been used as a luminescence probe for the calcium sites. Tb^{3+} is luminescent when bound to a protein near to a tyrosine residue, upon excitation of the latter. No significant increase in Tb^{3+} luminescence could be seen up to ratios of Tb^{3+}/calmodulin = 2/1, followed by a 400-fold enhancement of Tb^{3+} luminescence on further addition of Tb^{3+}. This suggests that the higher affinity sites under these conditions lack tyrosine, which identifies them as domains I and II.[219,228]

Deactivation of calmodulin-dependent enzymes may involve calmodulin-binding proteins such as calcineurin,[229] although calcineurin has been shown to possess phosphatase activity.[230]

The binding of calmodulin to target enzymes is an important topic. Several calmodulin-regulated enzymes have been purified: these include phosphorylase kinase, phosphodiesterase, calcineurin, (Ca^{2+}, Mg^{2+})-ATPase, troponin, fodrin and myosin kinases. Their calmodulin-binding subunits are all different from each other. Nevertheless, these subunits could share a common calmodulin-binding domain. However, while some enzymes bind calmodulin in the absence of Ca^{2+} (*e.g.* phosphorylase kinase, troponin I and bacterial adenylate cyclase), others cannot. This suggests that there is not a common interaction mode. The interaction sites have been investigated by several techniques. Cyclic nucleotide phosphodiesterase and the 3-(2-pyridyldithio)propionyl-substituted calmodulin crosslink[231] through the formation of —S—S— links to give an enzymatically active species in the absence of added Ca^{2+}. Such crosslinking techniques are useful for identifying specific sites on the enzyme which react with calmodulin.

Limited cleavage of calmodulin with trypsin to give large fragments allows these fragments to be tested for their ability to activate calmodulin-regulated enzymes and to bind anticalmodulin drugs. Trypsin digests in EGTA yielded peptides 1-106, 1-90 and 107-148. The fragment 1-106 contains sites I, II and III. Digests carried out in the presence of Ca^{2+} gave peptides 1-77 and 78-148, each of which contains two sites for calcium. The purified fragments contained <0.1% contamination by calmodulin. None of the fragments activated calcineurin nor prevented its stimulation by intact calmodulin. Nor did they stimulate cyclic AMP phosphodiesterase. However, the fragment 78-148 interacts with the phosphodiesterase, as shown by its ability to prevent activation by calmodulin. The same fragment can activate phosphorylase kinase.[232] This suggests the phosphorylase kinase is less exacting in its structural requirements for activation by calmodulin than the phosphodiesterase, and argues against the idea that calmodulin-activated enzymes share a common binding domain.

Calmodulin from *Tetrahymena* presents interesting contrasts to calmodulins purified from vertebrate sources, and has, for example, 11 amino acid substitutions and one deletion of an amino acid residue compared to bovine brain calmodulin. Most of these variant residues are located near or at the III and IV Ca^{2+}-binding sites. *Tetrahymena* calmodulin is very specific to

activate *Tetrahymena* guanylate cyclase. ^{43}Ca NMR studies show, however, that these changes in amino acid composition have little effect on the mobility of Ca^{2+} in *Tetrahymena* calmodulin.[233]

62.1.3.4.2 Troponin C

Muscle contraction is triggered by the binding of Ca^{2+} to the regulatory proteins present in the thin actin-containing filaments in muscle fibrils. Troponin is located at intervals of 38.5 nm along the thin filaments and is made up of three subunits. Troponin I (TN-I) inhibits the actomyosin ATPase, preventing muscle contraction; troponin T (TN-T) binds tropomyosin, while troponin C (TN-C) binds calcium. Binding of calcium causes a conformational change in TN-C, which is transmitted through TN-I and TN-T to tropomyosin which then undergoes conformational changes that allow the interaction of myosin and actin. The isolated subunits have been much studied, although binding to troponin is different from binding to TN-C.

Troponin C from rabbit skeletal and bovine cardiac muscle has a molecular weight of about 18 000. Skeletal TN-C has four sites for Ca^{2+}. Two of these (III and IV) are high affinity sites ($K \approx 10^7$ dm^3 mol^{-1}) which also bind Mg^{2+} competitively, with $K \approx 10^3$ dm^3 mol^{-1}. The remaining two (I and II) appear to be specific for Ca^{2+}, although of lower affinity ($K \approx 10^5$ dm^3 mol^{-1}).[234] These two sites are the only sites in calcium-binding proteins that do not bind Mg^{2+} with constants in the range 10^2–10^3 dm^3 mol^{-1}. Cardiac TN-C contains two Ca^{2+}–Mg^{2+} sites, one Ca^{2+}-specific site and one low affinity site for Ca^{2+}, in which the two aspartate residues in the skeletal TN-C protein are replaced by leucine and alanine residues.[235]

The Ca^{2+}-specific sites are involved in regulation,[236] a view that is supported by kinetic evidence. Calcium dissociates from the Ca^{2+}-specific sites with a $t_{1/2}$ of about 2 ms, and from the Ca^{2+}–Mg^{2+} sites with a $t_{1/2}$ of about 700 ms. The latter reaction is clearly too slow to be relevant to the regulation of muscle contraction,[237] and is even slower in the intact troponin complex.[238] It should be noted that metal exchange was not measured directly in these experiments, but rather a conformational change in the protein, which may or may not be correlated with the metal exchange. However, ^{43}Ca NMR studies are consistent with there being exchange at two sites, while the other two sites exchange too slowly to affect the shape of the observed ^{43}Ca NMR signal.[239]

Binding of cations to trypsin-produced fragments and synthetic peptide analogues of troponin C has been studied. Trypsin hydrolysis gives a fragment 85–134, which contains at least one of the high affinity Ca^{2+}–Mg^{2+} sites. The use of NMR techniques confirms that conformational changes occur on binding of calcium.[240] A synthetic 13-residue fragment has been synthesized, corresponding to residues 103–115, which contains site III.[241] Rather different conformational changes are induced by binding Lu^{3+} and La^{3+}, reflecting differences in ionic radii (Ca^{2+}, 1.00 Å; La^{3+}, 1.03 Å; Lu^{3+}, 0.86 Å). This is also shown in the binding constants ($K_{La^{3+}}$, 1.1×10^5; $K_{Lu^{3+}}$, 1.3×10^4, $K_{Ca^{2+}}$, 3×10^2 dm^3 mol^{-1}). The NMR results show that glycine-108 adopts a restricted geometry in the absence of metals, such that the two protons on the α-carbon atom are in different environments. This suggests that this highly conserved residue is important in controlling the peptide folding pattern associated with the EF hand (site III). Calcium-binding proteins without glycine-108 in the EF hand domain are the intestinal calcium-binding proteins and the S100 protein, which have distorted calcium-binding sites.[242]

Twelve-residue peptides have been synthesized as structural analogues of the 63–74 fragment, which contains the Ca^{2+}-specific binding site II. In one analogue, Phe-72 was replaced by tyrosine, and in the other Gly-66 was also substituted by serine. From the enhancement of Tb^{3+} emission, a 1:1 binding stoichiometry was confirmed, and association constants around 2×10^5 dm^3 mol^{-1} determined. NMR studies show that binding of La^{3+} induced considerable perturbation of the amide proton resonances of aspartate, tyrosine and glutamate residues.[243]

The calcium sites in troponin C have been studied by X-ray absorption near edge structure (XANES).[244] In all four cases, Ca^{2+} appears to be coordinated to carboxylate and carbonyl groups, and no structural differences could be found between the two classes of sites. Binding of Mg^{2+} causes a distortion of the geometry of the calcium site. Thus, the reduced affinity for Ca^{2+} of the Ca^{2+}–Mg^{2+} sites in the presence of Mg^{2+} may not simply be due to competition with Mg^{2+}, but due to some conformational change induced at these sites by Mg^{2+}. The similarity of all four Ca^{2+} sites means that local bonding effects do not explain the inability of Mg^{2+} to bind to the calcium-specific sites I and II. The XANES of parvalbumin differs from that of troponin C.

In summary, it may be that binding of calcium (or magnesium) to the Ca^{2+}–Mg^{2+} sites controls and stabilizes the structure of troponin C,[245,246] and that the binding of calcium to the calcium-specific sites causes more localized structural changes which serve to trigger muscle contraction.

62.1.3.4.3 Parvalbumins

These are soluble, sarcoplasmic calcium-binding proteins found in vertebrates. Invertebrates contain different sarcoplasmic calcium-binding proteins.[247] Parvalbumins are low molecular weight (10 000–12 000), acidic proteins which contain two binding sites for Ca^{2+}. The structure of parvalbumin has been determined, and details of the calcium sites are given in Table 6. XANES studies indicate that the calcium sites are similar to those in calmodulin, but different from troponin C.[244,248] The two parvalbumin sites have different coordination numbers, six and eight.[249]

The parvalbumins appear to function as regulators by helping to control calcium concentration levels or by removing calcium from troponin C. At physiological levels of Mg^{2+} (1 mmol dm^{-3}) and levels of Ca^{2+} corresponding to those of resting muscle (10^{-8} mol dm^{-3}), parvalbumin binds two Mg^{2+} per molecule. A rise in free [Ca^{2+}] results in release of Mg^{2+} and binding of Ca^{2+}. In the muscle cell, parvalbumin is therefore always cation bound. Thus, the only conformational changes of physiological significance are those that occur on Ca^{2+}–Mg^{2+} exchange, which appear to be very small and relate to the metal-binding sites.[250] Dissociation of Mg^{2+} from parvalbumin occurs with an off rate constant of about 10 s^{-1}. At the onset of contraction, Ca^{2+} will be liberated from the sarcoplasmic reticulum, but the sites on parvalbumin will be blocked by Mg^{2+}. Thus, the released Ca^{2+} will bind preferentially at the Ca^{2+}-specific sites on troponin C, and so trigger contraction. Later, the calcium sites on parvalbumin will be able to compete for Ca^{2+}, when the Mg^{2+} is dissociated. This will result in the removal of Ca^{2+} from troponin C and relaxation of the muscle.

62.1.3.4.4 Myosin light chains

Control of the actin–myosin interaction in smooth muscle results from phosphorylation and dephosphorylation of the myosin light chain. Phosphorylation is catalyzed by a myosin light chain kinase, a subunit of which is the Ca^{2+}-binding regulatory protein calmodulin.[251] However, it appears probable that there is a secondary regulatory mechanism, involving a troponin-like system or direct binding of Ca^{2+} to myosin. One of the difficulties here lies in distinguishing between such a protein and calmodulin, but recent work has produced evidence for a troponin-like regulatory system.[252]

62.1.3.4.5 Calcium-binding intestinal protein

This protein was first detected in the intestine of chick, and subsequently found to be widely distributed.[253,254] These are vitamin D-dependent proteins, in that their synthesis requires the presence of vitamin D. Indeed they are synthesized probably within an hour of exposure to vitamin D.[255] There appear to be two types of vitamin D-dependent calcium-binding proteins. In birds a 28 000 molecular weight protein, having four high affinity sites for calcium, is found in the intestine, kidney, brain, shell gland and other organs. A similar protein is found in certain tissues in mammals, but the main intestinal calcium-binding protein has a molecular weight of about 9000 and has two high affinity sites for calcium. Both proteins bind additional Ca^{2+} at sites of lower affinity. Binding constants are 2×10^6 dm^3 mol^{-1} with about 32 Ca^{2+} at low affinity sites having $K \approx 10^2$ dm^3 mol^{-1} (for chick protein); and 4.3×10^6 dm^3 mol^{-1} with two or three Ca^{2+} at low affinity sites (for bovine protein). The function of the protein is probably concerned with translocation of calcium in a range of cells including brain, pancreas and parathyroid. They are soluble proteins.

The structure of the bovine protein has been determined to 2.3 Å resolution (Table 6).[242] It contains a pair of calcium-binding domains similar to those in parvalbumin, but one domain has a longer and rearranged calcium-binding group. The intestinal calcium-binding protein has four helices wrapped around a hydrophobic core, with hydrophobic contacts between side-chains from all pairs of helices. The single tyrosine, Tyr-13, lies in a depression on the surface and is probably hydrogen bonded to Glu-35, thus linking helices I and II. Proposals[256] based on NMR data on the interaction of Tyr-13 with one Ile and two Phe residues in a hydrophobic pocket are confirmed. The calcium-binding loop between helices III and IV is extremely similar to parvalbumin, and both have a water molecule coordinated to Ca^{2+}. The I–II loop is rather different from that in parvalbumin, resulting partly from the presence of two additional residues. There are also significant differences between the conformations of the intestinal protein and parvalbumin.

Removal of Ca^{2+} results in a substantial conformational change. Thus crystals of the protein disintegrate in 1.0 mmol dm^{-3} EDTA, and crystals of the calcium-free protein cannot be grown. NMR studies had indicated that structural changes occurred on binding of calcium.[256]

By analogy with other calcium-binding proteins, it is expected that the Ca^{2+}-bound intestinal protein is then able to interact with some receptor protein. Suggestions have been made for interaction with alkaline phosphatase or carbonic anhydrase, but another possibility is that the calcium-bound protein is able to activate a gating mechanism for the transport of calcium.

62.1.3.4.6 S100 proteins

These are Ca^{2+}-binding proteins found in the brain and the central nervous system, which belong to the same branch of the calmodulin family as the intestinal proteins, to which they are closely related. Both contain one variant and one normal[211] site for Ca^{2+}. The S100 protein exists in two forms, a and b.[257] Binding of calcium results in conformational change. The S100b protein also binds two Zn^{2+} ions, with conformational change, and with higher affinity than Ca^{2+}.[258] Zn^{2+} is involved with the tubulin microtubule system in brain. S100b may be associated with this process.

62.1.3.4.7 Proteins with γ-carboxyglutamate residues

These important calcium-binding proteins[259,260] are vitamin K dependent, as their synthesis involves a vitamin K-dependent carboxylase, and requires O_2, reduced vitamin K and CO_2.[261] The carboxylation step is coupled to the formation of vitamin K 2,3-epoxide, and appears to have a high degree of specificity for glutamic acid residues. Aspartic acid residues have been carboxylated in synthetic peptides, but the only carboxylated product detected when using peptides with glutamyl and aspartyl residues was γ-carboxyglutamic acid.[262] The use of warfarin, a vitamin K antagonist, leads to the *in vivo* synthesis of defective proteins with uncarboxylated glutamyl residues. These are useful for mechanistic studies.

Table 8 Some 'gla' Proteins

Protein	*Function*	*Comment*
Prothrombin	Blood coagulation	Blood plasma
Factor IX	Blood coagulation	N-terminal region has 12 'gla' residues
Factor X	Blood coagulation	Light chain contains 12 'gla' residues
Factor VII	Blood coagulation	
Protein C	Inhibition of clotting	
Osteocalcin	Bone	
Urine proteins	Prevents precipitation[a] of calcium oxalate	

[a] Other proteins involved in the inhibition of precipitation have many tyrosine and proline residues.

Table 8 lists some examples of 'gla' proteins. They are associated, in particular, with the control of blood coagulation and calcification. These will be discussed in later sections (62.1.3.8 and 62.1.3.9). The precipitation of calcium oxalate in urine is inhibited by 'gla' proteins.[263]

A great deal of work has been done on complexes of γ-carboxyglutamate, and of small peptides containing single and di-γ-carboxyglutamate residues as models for the interaction of Ca^{2+} with 'gla' proteins. It appears that these are not useful predictors of metal-binding behaviour.[264–266]

62.1.3.4.8 Miscellaneous calcium-binding proteins

Calsequestrin is a calcium-storage protein found in the sacroplasmic reticulum, which binds about 50 calcium ions per monomer (molecular weight 40 000) with binding constants in the range 10^3–10^5 dm^3 mol^{-1}. Release and uptake of Ca^{2+} during muscle contraction and relaxation involve this store. Calsequestrin from rabbit skeletal muscle has a random coil conformation in the absence of calcium. Binding of Ca^{2+} is associated with a change to a more compact structure.[267]

Human saliva is supersaturated with basic calcium phosphate, to allow recalcification and protection of the dental enamel. Precipitation in the saliva is prevented by certain calcium binding proteins, which include statherin[268] (a 5380 molecular weight tyrosine-rich protein that also contains many proline and glutamic acid residues), and a group of proline-rich proteins.[269]

Calcium couples excitation to secretion in secretory cells and nerve endings. Inhibition of secretion by drugs such as trifluoperazine suggests the involvement of calmodulin. However, the process of exocytosis, which involves the fusion of a vesicle with the cell membrane and the ejection of its contents, is not activated by calmodulin. It is potentiated by synexin[270] and calelectrin.[271] Calelectrins are widespread in animal cells involving the calcium control of membrane transport. Chromogrannin A is a calcium-binding protein in chromaffin granules.

Ca^{2+} is also bound by certain polysaccharides, for example in coccolith formation by some unicellular organisms.

62.1.3.5 Mg^{2+} (Mn^{2+}) as Enzyme Activators

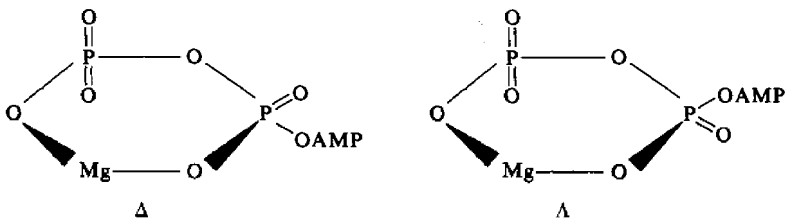
This section is concerned with enzymes that may be activated by Mg^{2+} or Mn^{2+}. These cations differ in their relative activity from enzyme to enzyme, and in at least one case regulation involves the conversion of an Mg^{2+}-specific site into an Mn^{2+}-specific site. Enzymes and proteins which have a specific requirement for manganese are considered in Section 62.1.3.6. In these cases the physiological requirement for manganese is not in question. In other cases, particularly where Mg^{2+} activates an enzyme to a similar or greater extent than Mn^{2+}, it is very difficult to imagine that manganese has a physiological role, as its concentration in cells is probably 100-fold less than that of magnesium. In many but not all cases, it is probably true that manganese stimulation of an (Mn^{2+}/Mg^{2+})-protein is an artefact of the assay conditions.

Table 9 Examples of Mg^{2+}-activated Enzymes

Type	*Function*	*Examples*	*Comment*
Kinases	Direct transfer of terminal phosphoryl group of ATP to substrate	Creatine kinase	Type 1 (M-S-E)
		Adenylate kinase	Type 1
		Hexokinase	Type 1
		Phosphoglycerate kinase	Type 1
		Pyruvate kinase	Type 2 (S-M-E)
		Protein kinase	
		Myokinase	
		Phosphofructokinase	
Phosphatase	Hydrolysis of phosphate	Inorganic pyrophosphatase (pyrophosphate $\rightleftharpoons$ orthophosphate $+PO_4^{3-}$)	
		Glucose-6-phosphatase	
		Fructose-1,6-bisphosphatase	Zn^{2+}
		Alkaline phosphatase	Zn^{2+}
		Phosphoprotein phosphatase	
	Translocation of ATPases linked to cation	(Na^+, K^+)-ATPase	Sodium pump
		(Mg^{2+}, Ca^{2+})-ATPase	Calcium pump
		Proton-translocating ATPase	H^+ pump
Mutase	Transfer of phosphoryl group between sites on substrate	Phosphoglucomutase (glucose-6-phosphate $\rightleftharpoons$ glucose-1-phosphate)	
Various hydrolytic functions		Citrate lyase (hydrolysis of citrate)	
		Succinyl-CoA synthetase	
		β-Galactosidase	
Biosynthetic processes	Elongation of RNA or DNA chains	RNA polymerase I	Zn^{2+}
		DNA polymerase	
		Poly(ADP-ribose)polymerase	
	Other synthetic routes	Carbamoyl phosphate synthetase	
		Anthranilate synthase–phosphoribosyl transferase	
		Glycogen synthetase	
		Methionyl-tRNA synthetase	
		ATP phosphoribosyl transferase	

Table 9 lists some Mg^{2+} (Mn^{2+})-activated enzymes. It is only possible to consider a representative selection in this section, but an attempt has been made to include examples of the main classes. Many of these enzymes are concerned with phosphate transfer and hydrolysis.

Adenosine triphosphate and adenosine diphosphate exist in cells largely as Mg^{II} chelates, since the intracellular [Mg^{2+}] levels are about 1 mmol dm^{-3}, and the dissociation constants for $MgATP^{2-}$ and $MgADP^{-}$ are 14 and 250 μmol dm^{-3} respectively. These Mg^{2+} complexes equilibrate rapidly and so, for example, the $MgATP^{2-}$ can exist as a number of coordination isomers. The two conformations possible for a β,γ-coordinated Mg^{2+}–ATP complex are shown in Figure 12. The β,γ-bidentate complexes of Cr^{III} and Co^{III} are substitution-inert analogues of $MgATP^{2-}$, and pure samples of the two isomers (Δ and Λ) may be prepared. Nucleotide-utilizing enzymes are highly specific for one of the two isomeric forms of these complexes,[273] if they serve as substrates. By analogy it is therefore possible to show the conformation of the magnesium nucleotide utilized as substrate. There are additional advantages in using Cr^{III} and Co^{III} complexes as analogues for $MgATP^{2-}$. The former species is a paramagnetic probe while the Co^{III} complex is diamagnetic and allows the application of NMR.



AMP = adenosine monophosphate

Figure 12 Coordination isomers of MgATP

As noted earlier, the binding of Mg^{2+} to ATP results in activation towards hydrolysis of the terminal phosphoryl group. Hydrolysis and transfer of phosphate may involve transfer of the phosphoryl group to the enzyme, followed by transfer to water or an acceptor molecule. Enzymes such as alkaline phosphatase and fructose-1,6-biphosphatase which require Mg^{2+} and Zn^{2+} will be considered in Section 62.1.4.

62.1.3.5.1 Kinases — some general comments

These catalyze the transfer of the terminal phosphoryl group of ATP to an acceptor species (equation 3). Kinases appear to involve a direct transfer of the phosphoryl group to the substrate. The ternary complex of enzyme, metal and substrate in the kinase may either be M-S-E (type I) or S-M-E (type II). Kinases which have a low metal ion specificity usually belong to type I, where the metal probably has the role of charge neutralization. In type II kinases, the metal has a role as a bridge and the requirement for metal is more precise. This classification is due to Cohn, and involved the use of Mn^{II} as a probe, NMR and ESR techniques and spin labels. Thus, for type I kinases, the MnADP binary complex has an ESR spectrum which does not change on formation of the ternary complex with enzyme. This shows that the Mn^{II} cannot be bridging. The existence of ternary complexes of type II (S-M-E) with bridging metal was shown by NMR studies on the proton relaxation rate of water bound to Mn^{2+}. Deenhancement of relaxation upon binding of substrate was consistent with substrate substitution into the coordination shell of Mn^{II} with replacement of water.[274,275]

$$ATP^{4-} + HX \overset{M^{2+}}{\rightleftharpoons} ADP^{3-} + XPO_3^{2-} + H^+ \qquad (3)$$

Kinetic studies on ADP-creatine kinase show the rate constants for association and dissociation of M-S and enzyme are practically independent of the nature of the metal, implying that the metal is not bridging and that this is a type I kinase.[276]

Replacement of Mg^{2+} by Mn^{2+}, ATP by CrATP and the use of spin labels have allowed the active sites in some of these reactions to be defined in terms of distance measurements between one of these paramagnetic centres and an appropriate magnetic nucleus in the substrate (^1H, ^{31}P or ^{13}C)[277-279] using NMR techniques.

62.1.3.5.2 Pyruvate kinase

Pyruvate kinase is a key enzyme in the important process of glycolysis, and its product, pyruvate, is passed into the Krebs' cycle. As noted in Section 62.1.2.3.1, pyruvate requires two divalent cations and one monovalent cation for activity. These are usually Mg^{2+} and K^+. The crystal structure of the enzyme from cat muscle has been determined to a resolution of 2.6 Å.[280]

A great deal of work has been carried out using NMR techniques coupled to the use of probes: Tl^+ for K^+; Mn^{2+} for Mg^{2+}; CrATP for $MgATP^-$ and spin labels. A model for the active site has been put forward based upon 15 distance measurements using four active complexes of pyruvate kinase (Figure 8).[281] This suggests contact between the phosphorus of the γ-phosphoryl group of ATP and the carbonyl oxygen of pyruvate, and supports direct phosphoryl-group transfer from ATP to substrate (and for the reverse reaction), in accord with the crystallographic studies. Pyruvate kinase is a type II kinase. Mn^{2+} bridges enzyme and substrate, while Tl^+ bridges the carboxyl group of phosphoenolpyruvate and the enzyme. The distance between Mn^{2+} and Cr^{III} in the Mn^{2+}-enzyme-Cr^{III}ATP complex is 5.2 ± 0.9 Å, showing van der Waals contact between the hydration spheres of enzyme- and nucleotide-bound metal ions. A detailed review of magnetic resonance studies on pyruvate is available.[282]

The Δ isomer of β,γ-bidentate CrATP is the only form of this complex which activates the phosphoryl-transfer reaction of pyruvate kinase.[281]

62.1.3.5.3 Miscellaneous kinases

Creatine kinase is a dimer (molecular weight 82 000), with an active site on each monomer. The activating metal binds to the ATP only, *i.e.* type I. Spin labelling of the cysteine residue at the active site has allowed distance measurements to Mn^{II}. It appears that Mn^{II} remains bound to the α- and β-phosphoryl groups in ADP.

Phosphoglycerate kinase is also an enzyme of the glycolytic pathway. It catalyzes the conversion of 1,3-diphosphoglycerate into 3-phosphoglycerate with production of ATP from ADP. It differs from most other type I kinases in that there is a substantial synergism in the binding of metal ion and nucleotide to the enzyme in the ternary complex. The metal nucleotide binds to the enzyme about two orders of magnitude more tightly than the free nucleotide.[283] A high-resolution crystal structure[284] shows the enzyme to be a single polypeptide chain organized into two widely separated domains of almost equal size. The binding site for the magnesium-nucleotide complex has been established, but the only reasonable site for the phosphoglycerate was 10 Å away at the N-terminal domain. One explanation to account for the coming together of the two substrates and the necessary exclusion of water from the site to prevent hydrolysis is that a 'hinge bending' conformational change occurs on binding of phosphoglycerate. This brings together the two substrates and expels the solvent. A similar mechanism has been suggested for hexokinase,[285] which catalyzes the phosphorylation of glucose by ATP.

Distance measurements on the CrADP, glucose 6-phosphate, yeast hexokinase complex confirm the absence of direct coordination of the phosphoryl group of glucose 6-phosphate to the nucleotide-bound metal, but indicate that there is van der Waals' contact between a phosphoryl oxygen of glucose 6-phosphate and the hydration sphere of the ADP-bound metal ion.[286]

Many other kinases have been studied, often in the context of regulation of some process by phosphorylation and dephosphorylation. Examples from muscle regulation have already been given. A further example is the transcription of eukaryotic DNA, which may be regulated by phosphorylation of non-histone chromosomal proteins. A number of nuclear protein kinases have been partially purified. These have an absolute requirement for divalent cations, and are not stimulated by 3′,5′-cyclic AMP (cAMP).[287,288]

A catalytic subunit from cAMP-dependent protein kinase from bovine heart binds Mn^{2+} with low affinity only in the absence of nucleotide. However, in the presence of nucleotide, a high affinity M^{2+} site was provided on the nucleotide and a lower affinity site on the protein. As both Mg^{2+} and Mn^{2+} inhibit at higher concentration it may be that binding at this site causes inhibition. Affinity for nucleotide increased by several orders of magnitude when the lower affinity site was filled.[289]

62.1.3.5.4 Phosphatases

These enzymes catalyze the hydrolysis of phosphates. Phosphatases requiring Mg^{2+} and Zn^{2+} for activity are discussed in Section 62.1.4. ATPase activity associated with the sodium and calcium pumps is covered in Sections 62.1.2.2.2 and 62.1.3.3.1.

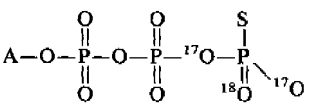
The hydrolysis of pyrophosphate to phosphate is catalyzed by yeast inorganic pyrophosphatase, which is a dimeric enzyme having two identical subunits.[290] It now appears that three cations are required per active site, two bound to the enzyme and the third to the phosphate (equation 4).

$$MgPP_i + Mg_2E \rightleftharpoons Mg_2EMgPP_i \rightleftharpoons MgE(MgP_i)_2 \rightleftharpoons MgEMgP_i + MgP_i \rightleftharpoons Mg_2E + P_i \quad (4)$$

There seems to be a specific requirement for Mg^{2+}, as it is much more effective than other divalent cations, the sequence being $Mg^{2+} \gg Zn^{2+} > Co^{2+}$, $Mn^{2+} \gg Cd^{2+}$. This is due to the slower rate of release of inorganic phosphate from the enzyme in the presence of cations other than Mg^{2+}, and reflects the high lability of Mg^{2+}-oxygen bonds.[291]

The use of NMR and ESR techniques with Mn^{2+} probes shows that the two Mn^{2+} ions bound to the enzyme are close enough to interact magnetically (10–14 Å). This separation decreases to 7–9 Å on binding diamagnetic substrate analogues. The use of Cr^{III} imidodiphosphate shows the Mn^{2+}–Cr^{3+} distance to be about 7 Å, suggesting all these metal ions are bound at the catalytic site.[292]

There is evidence (but not conclusive evidence) that the mechanisms involves direct phosphoryl transfer to water rather than the formation of a phosphoenzyme intermediate.[293] This utilizes the fact that ATP also serves as a substrate to inorganic pyrophosphatase. Hydrolysis of the ATP analogue adenosine 5′-*O*-(3-thiotriphosphate) chirally labelled with ^{17}O and ^{18}O at the γ-phosphate proceeds with inversion of configuration to give the chiral [^{17}O,^{18}O]-thiophosphate (Figure 13).[293]



A = adenosine

Figure 13 The structure of the ATP analogue adenosine 5′-*O*-(3-thiotriphosphate)

Several phosphoprotein phosphatases have been isolated. They show a range of relative activities towards Mn^{2+} and Mg^{2+},[294–296] while some are Mn^{2+}-specific.[297]

Extensive studies have been carried out on the proton-translocating ATPase of mitochondrial, bacterial and chloroplast membranes. This enzyme can also function in reverse to exploit the electrochemical potential of protons built up by respiration for the synthesis of ATP from ADP and P_i.[298] The synthesis of ATP can be effected by the application of external electrical pulses to the ATPase vesicles in suspension with submitochondrial particles, showing that the diffusion potential of the protons (ΔpH) is not used. The yield of ATP was linearly dependent on the number of pulses.[299]

The Mg^{2+}-activated ATPase (or ATP synthase) is made up of two parts. The F_1 component is the catalytic, Mg^{2+}-binding, extrinsic membrane protein composed of five different subunits, α, β, γ, δ and ε. The F_0 component is an intrinsic membrane complex that contains three subunits, a, b and c, and mediates proton translocation. The F_1 protein is bound to the membrane through interaction with F_0. The complexity of the F_1F_0 enzyme has presented many difficulties. The greatest advances have been made for the bacterial enzymes, notably for thermophiles, *Escherichia coli* and *Rhodospirillum rubrum*, where progress has been made in the purification of subunits and their reconstitution into membranes, and the identification of binding sites for Mg^{2+} and nucleotides on the F_1 subunits.[300] F_1F_0 preparations can be incorporated into liposomes and display H^+ translocation, ATP–P_i exchange and ATP synthesis.[301]

All five subunits of the *E. coli* F_1 ATPase have been purified, and the primary sequence of the α-subunit has been determined. ATPase activity could be reconstituted from the α-, β- and γ-subunits. Subunits β and γ from *R. rubrum* have been purified and reincorporated into the depleted membrane with full activity.[302] The α- and β-subunits contain sites for nucleotides.[303] The sensitivity of the α-subunit of *E. coli* to trypsin hydrolysis differs when the high affinity site for ATP is saturated, suggesting that binding of ATP produces conformational changes.[304]

Beef heart mitochondrial F_1ATPase binds one Mg^{2+}, probably at a structural site, and binds a second on incubation with ATP and $MgSO_4$, which probably has a catalytic role. The second Mg^{2+} can be replaced by Zn^{2+}, Mn^{2+} or Co^{2+}.[305] Plots of log k against $1/T$ are metal ion dependent, and may be linear or show discontinuities.[306] The rate-limiting step in the hydrolysis appears to be release of ADP from the enzyme.[307]

The three subunits of the F_0 component have been much studied. Their properties have been reviewed briefly.[308] Subunit c is thought to be the proton-translocating protein, as it binds the inhibitor DCCD, which blocks proton translocation, at a single carboxyl group. Indeed H^+

translocation in *E. coli* is abolished by substitution of this aspartate residue by glycine or asparagine. However, the purified subunit c cannot catalyze proton translocation in reconstituted membranes, although there are many explanations for this, possibly the requirement for correct oligomer formation which may involve the other F_0 subunits. It is probably an oversimplification to view the F_0 protein purely as a proton translocator. It could well have a role in the overall catalytic process.[309] Binding of protons to the specific carboxylate groups in the oligomeric form of protein subunit c in the membrane could result in a twisting of its helices, so that a conformational change is transmitted to the ATP site in the F_1 protein.[309]

62.1.3.5.5 Phosphate transfer and biosynthesis

Phosphoglucomutase catalyzes the interconversion of glucose 1-phosphate and glucose 6-phosphate *via* a phosphoenzyme intermediate in which the phosphate is bound to a serine residue at the active site. The Mg^{2+} is not bound to the phosphate, but studies with the Ni^{II}-substituted enzyme suggest the presence of a second-sphere complex between phosphate and metal, which could ensure correct positioning of the phosphoryl group for nucleophilic attack, as shown in Figure 14.[278]

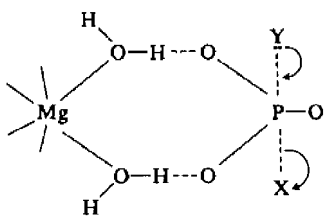


Figure 14 The second-sphere complex between Mg^{2+} and substrate in phosphoglucomutase

Enzyme I from *E. coli* catalyzes the transfer of a phosphoryl group from phosphoenolpyruvate to a phospho carrier protein (HPr). A phosphoryl group is transferred to a dimeric form of the enzyme. Mg^{2+} or Mn^{2+} is necessary for stabilization of the dimer and for activity, although it is not known whether these functions are carried out at separate sites.[310] A scheme is shown in equations (5) and (6).

$$2E_I^m \rightleftharpoons E_I^d \underset{-PEP}{\overset{PEP}{\rightleftharpoons}} E_I^dP + \text{pyruvate} \quad (5)$$

$$E_I^dP + HPr \rightleftharpoons PHPr + E_I^d \quad (6)$$

The first two steps in the biosynthesis of tryptophan in *Salmonella typhimurium* involve the enzyme complex anthranilate synthase-phosphoribosyltransferase, which is a tetramer having two subunits of each enzyme. The anthranilate synthase catalyzes reaction (7) and the phosphoribosyltransferase catalyzes two reactions: the N-terminal portion cleaves glutamine to glutamate giving NH_3 for the anthranilate synthase, while the C-terminal portion catalyzes reaction (8).[311,312] All these reactions require M^{2+} cations. Orotate phosphoribosyltransferase binds four Mn^{2+} ions in a cooperative fashion; kinetic data have been interpreted in a scheme where both metal-free and metal-containing enzyme catalyze the reaction.[313]

$$\text{chorismate} + NH_3 \xrightarrow{M^{2+}} \text{anthranilate} + \text{pyruvate} + H^+ \quad (7)$$

$$\text{anthranilate} + \text{5-phosphoribosyl-1-pyrophosphate} \xrightarrow{M^{2+}} \textit{N}\text{-(5'-phosphoribosyl)anthranilate} + PP_i \quad (8)$$

$$NH_3 + \text{glutamic acid} + ATP \rightarrow \text{glutamine} + ADP + P_i \quad (9)$$

Glutamine synthetase is a key enzyme in nitrogen metabolism,[314] and catalyzes reaction (9). The enzymes from *E. coli*,[314] *S. typhimurium*[315] and *Azotobacter vinelandii*[316] are dodecameric, and involve a symmetrical aggregate of the 12 subunits (each of molecular weight 50 000–56 000) in two hexagonal layers. In Gram-negative bacteria, but not in blue-green algae, the enzyme is regulated by a covalent adenylylation of a tyrosine residue in each subunit. This converts an Mg^{2+}-specific site into an Mn^{2+}-specific site, with decrease in activity. Glutamine synthetase from

rat liver has subunit molecular weights of about 43 000 and does not show adenylylation control.[317]

There are two cation-binding sites per subunit, classified n_1 and n_2. The n_1 site is a structural site, which may involve the reorientation of a glutamate carboxyl group. Metals bind first at this site. The n_2 site is the catalytic site and may bind metal or metal-nucleotide. Co^{III} and Cr^{III} can be incorporated into the n_1 metal-binding sites in un-adenylylated glutamine synthetase from *E. coli*.[318] Both derivatives were inactive, but were able to bind Mn^{2+} at the n_2 site. Comparison of the quaternary enzyme-Cr^{III}-Mn^{II}-ADP (which shows spin-spin interaction between the two metal centres) with enzyme-Co^{III}-Mn^{II}-ADP leads to an estimate of the distance between n_1 and n_2 sites of 7 ± 2 Å.

Mn^{2+} binds to the n_1 site and binds a glutamate analogue methionine-(SR)-sulfoximine (MSox), which also perturbs the environment of Mn^{2+} at the n_2 site. CrATP will bind to enzyme-Mn-MSox. A number of distance measurements are available,[94] while various considerations suggest that CrATP and MnATP interact differently at n_2, with the Mn^{2+} only being bound to the protein. These structures are shown in Figure 15.

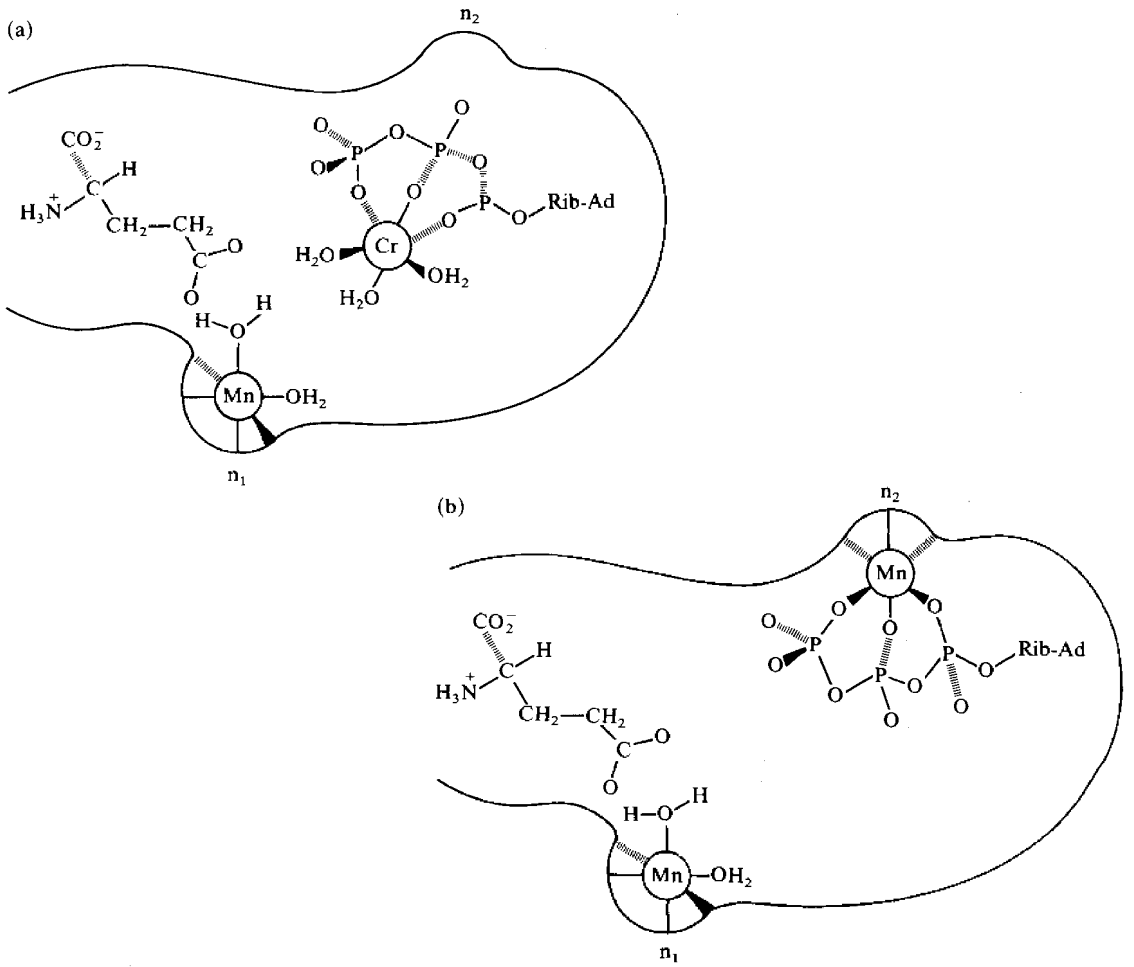


Figure 15 Model for glutamine synthetase showing the binding of (a) CrATP and (b) MnATP to the catalytic site [reproduced with permission from J. J. Villafranca and F. M. Raushel, 'NMR and EPR Investigations of Bi-Metalloenzymes' (*Adv. Inorg. Biochem.*, 1982, **4**, 316), Elsevier, Amsterdam]

Most glucose isomerases require metals for activation, Mg^{2+}, Mn^{2+} or in some cases Co^{2+}. Mg^{2+} and Co^{2+} seem to compete for the same site in glucose isomerase from *Streptomyces griseofuscus* S-41. Mg^{2+} was a better activator, but Co^{2+} conferred greater heat stability and resistance to acid inactivation and to denaturation. Four Co^{2+} ions are bound, but three can be removed by treatment with EDTA. The remaining Co^{2+} seems to be tightly bound and to have a role in stabilizing the enzyme configuration.[319]

Yeast enolase is a dimeric enzyme that requires divalent cations for catalytic activity.[320] Two Mg^{2+} ions bind tightly to the apoenzyme in the absence of substrate, while two more bind in the presence of substrate. The former sites are 'structural', binding of Mg^{2+} producing changes in the UV and CD spectra, while the latter sites are catalytic. Four Co^{2+} ions bind per dimer in the absence or presence of substrate, although binding is tighter in the presence of substrate. The binding or the first two ions produces conformational change. Both visible and ESR spectra show that the two classes of site provide different geometries for the cobalt(II). Cobalt at the structural site appears to be in a tetragonally distorted octahedral environment, while the second pair of cobalt ions appears to be in a site of more regular tetrahedral symmetry. The addition of Mg^{2+} or substrate to the enzyme with only one pair of cobalt ions per dimer causes striking conformational changes in the environment of the metal. It appears that interactions between the subunits allow the third ion per dimer to be activating and cause inhibition of the enzyme when the fourth site is filled.[321] Other workers have reported the binding of six Co^{2+} or Zn^{2+}, with the last two causing inhibition.[322] Studies on the copper-substituted enzyme show that the two types of site are close to each other.[323] In contrast to these studies, Tb^{III} binds only to the structural sites, even in the presence of the substrate. If Tb^{III} does bind then it does so at sites that do not include carboxyl groups.[324]

Citrate lyase catalyzes the cleavage of citrate to oxaloacetate and acetate in the presence of Mg^{2+} or Mn^{2+}, but in the presence of EDTA it catalyzes its synthesis. The enzyme is a complex of three subunits. The γ-subunit functions as an acyl carrier protein (ACP). The α-subunit is an acyl transferase involved in citryl-ACP formation and the release of acetate, and the β-subunit catalyzes the cleavage of the citryl-ACP intermediate to oxaloacetate and acetyl-ACP. The enzyme from *Klebsiella aerogenes* has been purified, and binds 18 Mn^{2+} in a cooperative manner.

62.1.3.5.6 Nucleotide cyclases

Adenylate cyclase and guanylate cyclase have a central role in mediating cellular responses through the formation of cAMP and cGMP respectively. They are activated by Mn^{2+} or Mg^{2+}. For guanylate cyclase Mn^{2+} is most effective, but the reverse is sometimes the case for adenylate cyclase for which the relative effectiveness of these two cations can vary with pH. The substrate for adenylate cyclase appears to be the Mg^{2+} or Mn^{2+} complex of ATP because ATP in excess of divalent cation is inhibitory.[326] However, addition of cation over the concentration needed to complex the substrate enhances activity, probably by binding to the protein itself.[327] Adenylate cyclase from brain has an absolute requirement for free Mg^{2+} ions, but the addition of 0.5 mmol dm^{-3} Mn^{2+} stimulated the enzyme, for example by halving the K_m value for Mg^{2+} and by increasing V_{max}.[328]

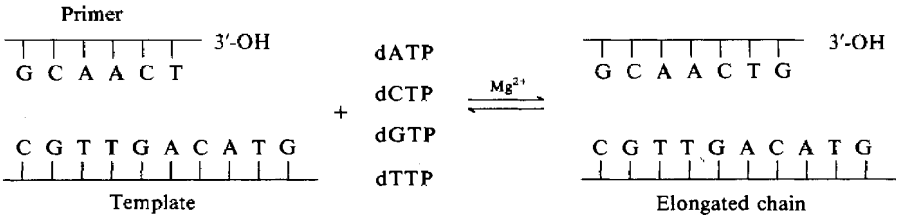
Limited proteolysis by thermolysin, papain, subtilsin and α-chymotrypsin of the plasma-membrane-bound adenylate cyclase from rat liver had no effect on activity when Mn^{2+} was the cofactor, but stimulated activity in the presence of Mg^{2+}. However, the addition of Mg^{2+} over MnATP did not result in stimulation on proteolysis. The simplest interpretation is that proteolysis exerts its main effect on the regulatory components of adenylate cyclase.[329] Adenylate cyclase, solubilized from rat liver membranes by Lubrol PX or deoxycholate, loses its regulatory components, and becomes much more specific for MnATP.[330]

The functions of guanylate cyclase and cGMP have been reviewed.[331] The soluble form of the enzyme has been purified from rat liver[332] and rat lung.[333] Both have a molecular weight of about 150 000 and are activated about 10 times more effectively by Mn^{2+} than Mg^{2+}.

62.1.3.5.7 DNA and RNA polymerases

These enzymes catalyze the replication and transcription of DNA, and have a specific requirement for Mg^{2+} or Mn^{2+}.[99] Both enzymes have been thought to require Zn^{2+} in addition,[334,335] in accord with the well-known effect of zinc deficiency on *Euglena gracilis*, which results in defects in synthesis of nucleic acids and proteins, and in cell division. However, it appears now that the DNA polymerase is not a zinc enzyme.[336]

The DNA polymerase is responsible for the accurate copying of a polynucleotide template. It catalyzes nucleophilic attack of the 3′-OH terminus on the α-phosphorus of a deoxynucleoside triphosphate, with displacement of pyrophosphate and incorporation of the nucleoside into the elongating DNA. The reaction involves a template-primer complex and the availability of all



A = adenine, C = cytosine, G = guanine, T = thymine

Figure 16 The action of DNA polymerase

four deoxynucleotide substrates, and is represented in Figure 16. The DNA polymerase I, in phosphate buffer, has one binding site each for the template, substrate and the deoxynucleoside monophosphate.

The binding of Mg^{2+} or Mn^{2+} has been characterized by the use of ESR in the manganese case. This shows one tight-binding active site, four intermediate sites, and additional sites of low affinity that cause inhibition when occupied by Mn^{2+}. Both tight and intermediate sites have to be occupied for activity in the case of Mg^{2+}. A study[337] of relaxation rates of phosphorus and hydrogen atoms in the bound dTTP substrate with Mn^{2+} at the active site has allowed distance measurements to be made for both the binary Mn-dTTP complex and the ternary DNA polymerase-Mn-dTTP complex. This has allowed the structures shown in Figure 17 to be proposed.

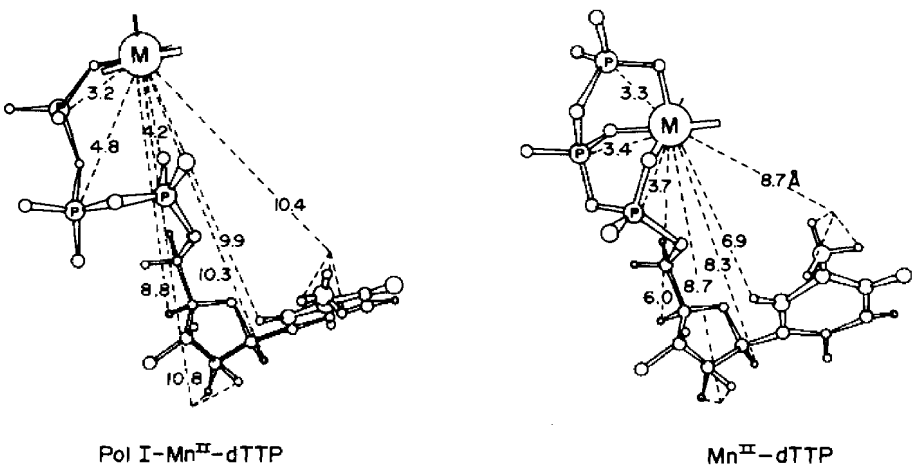


Figure 17 Structure of the Mn-dTTP and DNA polymerase-Mn-dTTP complexes; distances are in Å (reproduced with permission from *J. Biol. Chem.*, 1975, **250**, 8913

There are two main differences between the binary and ternary complexes. In the binary complex, all three phosphoryl groups of dTTP are coordinated to Mn^{2+}, but in the ternary complex with the DNA polymerase only the γ-phosphoryl group remains coordinated, while Mn—β-P and Mn—α-P distances are 4.9 and 4.2 Å respectively. The cation has the role of linking the enzyme to the γ-phosphoryl group of the substrate to assist the leaving of the pyrophosphate group.

The second difference concerns the conformation about the thymine-deoxyribose bond of dTTP, which in the ternary complex has the configuration corresponding to a nucleotidyl unit in the product, *i.e.* double helical DNA. This may represent an error-preventing mechanism.[338]

The RNA polymerases are more complex.[339] They contain two Zn^{2+} per molecule, although additional zinc may bind at the Mg^{2+} site with inhibition. There may well be multiple roles for Zn^{2+}, both structural and catalytic. The two sites in the enzyme from *B. subtilis* have different[340] affinities for Zn^{2+}, in accord with this proposition. The enzyme from *E. coli* has at least five subunits. Zn^{2+} is located on the subunit which binds DNA and on the subunit on which the initiation and elongation nucleotide binding sites are located.[341]

There is also a requirement for Mg^{2+} or Mn^{2+}. ESR studies with Mn^{2+} show one tight site and about six sites of low affinity. The one tight site is involved in the active site for RNA chain elongation,[342] but the function of the other sites is not known. The nucleotide analogue CrATP

binds at the initiation site. The presence of two paramagnetic centres has allowed some distance measurements to be made. Thus the Mn^{2+} is 4.0–5.7 Å from the substrate site and 9.0–10.5 Å from the initiation site, while the substrate site is 7.9–11.0 Å from the initiator site.[99]

There appear to be subtle variations once more on the Mg^{2+}/Mn^{2+} theme. The RNA polymerase II from the edible mushroom *Agaricus bisporus*[343] cannot be activated by Mg^{2+} and requires Mn^{2+} specifically. RNA polymerase A from *Saccharomyces cerevisiae*[344] and RNA polymerase I from wheat germ[345] require Mn^{2+} for the initiation step of synthesis of RNA, but Mg^{2+} and Mn^{2+} were equally effective in the elongation step.

There is also some interplay between the Zn^{2+} and Mn^{2+} cations. The RNA polymerase isolated from *Euglena gracilis* grown on a zinc-deficient medium contains two Zn^{2+} per molecule but differs from the RNA polymerases isolated from zinc-sufficient cells. The messenger RNA from the zinc-deficient cells had a different base composition, with a two-fold increase in the (G+C)/(A+U) ratio. Since intracellular $[Mn^{2+}]$ increases in zinc-deficient cells, the effect of $[Mn^{2+}]$ on the RNA polymerase from zinc-deficient cells was investigated. It was shown that increased levels of Mn^{2+} lead to increased incorporation of GMP relative to UMP.[346]

It should be noted that zinc deficiency in *E. gracilis*, which affects the metabolism of the RNA polymerases and DNA, also results in the modification in type and amount of the chromatin proteins. All the histones are absent in stationary phase cells.[347]

62.1.3.6 Proteins and Enzymes with a Specific Requirement for Manganese

It has been seen that some enzymes require Mg^{2+} or Mn^{2+} for activation, and that while, in certain cases, there appears to be high specificity for Mn^{2+} over Mg^2 there is still doubt over the physiological requirement for manganese. This section is devoted to the consideration of enzymes which bind manganese tightly and which without doubt are specific for manganese. Some of these examples are redox active, such as pseudocatalase, manganese superoxide dismutase, ribonucleotide reductase and the dioxygen-evolving centre in photosystem II. The resting pseudocatalase and superoxide dismutase involve Mn^{III}, as does the purple acid phosphatase. In these three cases, and in ribonucleotide reductase, manganese seems to act as functional catalytic counterpart to iron. Pseudocatalase, manganese superoxide dismutase and the mangano protein of photosystem

Table 10 Proteins and Enzymes with a Specific Requirement for Manganese

System	*Comment*	*Ref.*
Pseudocatalase	*Lactobacillus plantarum* Mn^{III}	1
Superoxide dismutase	Mn^{III}	2
Photosystem II	O_2 evolution in photosynthesis	3
Ribonucleotide reductase	*Brevibacterium ammoniagenes*	4, 5
Acid phosphatase	Mn^{III}	6
Lectins: concanavalin	Saccharide binding	7
LBL_4	Lima beans, tetramer	8
LBL_8	Octamer	
Phosphoglycerate phosphomutase		9
Phosphoenolpyruvate carboxykinase		10
Galactosyl transferase		11
Glucosyl transferase		12
Arginase		13
Phosphoprotein phosphatase		14

1. Y. Kono and I. Fridovich, *J. Biol. Chem.*, 1983, **258**, 6015.
2. J. J. Harris, in 'Superoxide and Superoxide Dismutases', ed. A. M. Michelson, J. M. McCord and I. Fridovich, Academic, New York, 1977, p. 150.
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6. S. Fujimoto, A. Ohara and K. Uehara, *Agric. Biol. Chem.*, 1980, **44**, 1659.
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10. M. J. Macdonald, L. A. Bentle and H. A. Lardy, *J. Biol. Chem.*, 1978, **253**, 116.
11. J. E. Chustner, J. J. Distler and G. W. Jourdian, *Arch. Biochem. Biophys.*, 1979, **192**, 548.
12. R. Myllyta, H. Anttinen and K. I. Kivirikko, *Eur. J. Biochem.*, 1979, **101**, 261.
13. H. Kadowaki and M. C. Nesheim, *Int. J. Biochem.*, 1979, **10**, 303.
14. A. Burchell and P. Cohen, *Biochem. Soc. Trans.*, 1978, **6**, 220.

II will be discussed in Sections 62.1.12.9.6, 62.1.12.8.2 and 62.1.3.7 respectively. Table 10 lists proteins and enzymes which have a specific requirement for manganese.

Reviews are available on the physiology and biochemistry of manganese in mammals[348] and on manganese nutrition in ruminants.[349] Manganese is bound in serum as an Mn^{III} β_1 globulin and in erythrocytes as a manganese porphyrin. It is present in rat serum as manganese transferrin. These again emphasize similarities with iron.

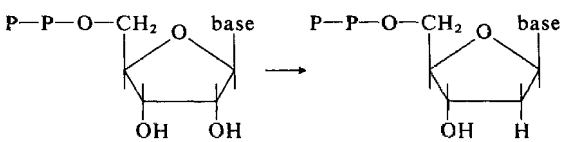
62.1.3.6.1 Tyrosine-bound manganese: purple manganese acid phosphatase and ribonucleotide reductase

Purple, iron-containing acid phosphatases have been purified from animal sources and from some plant sources.[350] However, the purple acid phosphatase from the sweet potato contains manganese, the purple colour arising from an intense absorption band at about 515 nm. There is some doubt over the stoichiometry, in that the dimeric enzyme may contain one[351] or two[352] Mn^{2+}, apparently depending on the variety of sweet potato. The iron acid phosphatases contain two Fe atoms.

It appears that the manganese (and iron) acid phosphatase belongs to the group of metal-tyrosinate proteins whose importance is receiving increasing recognition. Resonance Raman studies have shown the coordination of a tyrosine phenolate anion[353] to the Mn^{III} centre. The spectrum of the protein in which tryptophan residues have been modified to overcome fluorescence problems shows a band at 370 cm^{-1}, which has been assigned to an Mn^{III}–S stretching mode.[354] There is chemical evidence for a cysteine residue at the active site.

The Mn^{III} acid phosphatases have an intense band in the visible spectrum at 515–570 nm, assigned to tyrosine-Mn^{III} charge transfer. Unlike the iron proteins, they do not require mild reduction for maximum activity. The linear relation between the intensity of absorption at 515 nm and phosphatase activity indicates that the metal is essential for catalysis. Neither manganese protein shows a room temperature ESR spectrum, but on acid denaturation they show a spectrum characteristic of high-spin Mn^{II}. Little is known at present about the mechanism of these reactions.

Reduction of ribonucleotides to the deoxyribonucleotide is the first step on the pathway to DNA (equation 10). The ribonucleotide reductases utilize redox active SH groups, in association either with an adenosylcobalamin prosthetic group (for triphosphates) or a dimeric iron centre involving a stable tyrosine free radical (for diphosphates). Both situations will be discussed later. However, it appears that there is a manganese analogue of the iron-containing ribonucleotide reductase. *Brevibacterium ammoniagenes* ceases to synthesize DNA in manganese-depleted media, and ribonucleotides are accumulated in the media. The inactive ribonucleotide reductase extracted from cells grown under these conditions is reactivated by Mn^{2+}. Fe^{2+} can replace Mn^{2+} with about half efficiency, while Co^{2+} and Zn^{2+} are inactive.[355]



(10)

62.1.3.6.2 Concanavalin A and other lectins

The lectins are saccharide-binding proteins, of which concanavalin A from the jack bean is best studied. It exists in dimeric and tetrameric forms below pH 6 and above pH 7 respectively. Each subunit (molecular weight 27 000) contains a saccharide-binding site, an Mn^{2+} site (S_1) and a calcium-binding site (S_2). Other transition metals may bind at S_1. The X-ray structure of apo-Con A has been reported by two independent groups.[356,357] This work allows an understanding of the transformation of apo-Con A into the saccharide-binding form on the addition of metals. It appears that Mn^{2+} binds first, with deprotonation of His-24 and the breaking of the salt bridge to Asp-19. This allows the carboxyl group of Asp-19 to take up a position appropriate for coordination to Ca^{2+} in S_2. Furthermore the peptide bond between Ala-207 and Asp-208, which is in the *cis* position in the holoprotein, appears to have isomerized to the *trans* conformation in the apoprotein. This region is associated with carbohydrate binding. The kinetics of transformation

of apo-Con A into the locked saccharide-binding form can be followed by monitoring the quenching of fluorescence of 4-methylumbelliferyl α-D-mannopyranoside. The results appear to be consistent with a rapid equilibrium between bound and free metal ion, followed by slow irreversible change in conformation of the protein,[358] but there is still some uncertainty on this matter,[359] and it may be possible to prepare a metastable form of apo-Con A in the locked form.

All the direct metal ligands in Con A are retained in the lectin from favin,[360] which also binds stoichiometric amounts of Mn^{2+} and Ca^{2+}. In total, about 40% of the residues are identical, including the site of the proposed *cis–trans* isomerization underlying the 'locked' to 'unlocked' conformational change. It will be of interest to compare the kinetics of binding of metals to favin with the results from Con A.

62.1.3.6.3 Phosphoenolpyruvate carboxykinase

The cytosolic isozyme from bullfrog liver has an absolute requirement for Mn^{2+}.[361] In enzymes from other sources, Fe^{2+} can serve as an activator instead of Mn^{2+} provided an additional protein, ferroactivator, is present.[362] Ferroactivator had no effect on the Mn^{2+}-stimulated enzyme.

62.1.3.6.4 Phosphoglycerate phosphomutase

The enzymes isolated from *Bacillus* have a unique requirement for manganese. Thus the *Bacillus subtilis* enzyme[363] is absolutely dependent on Mn^{2+} and is unaffected by Mg^{2+}, Ca^{2+} or Fe^{3+}. The enzyme isolated from spores appeared to be identical to the one isolated from vegetative cells, and to require Mn^{2+} for activity. Developing spores of *B. megaterium* accumulate the substrate of this enzyme, 3-phosphoglyceric acid (PGA), apparently as the energy source for the germinating spore. Therefore, phosphoglycerate phosphomutase must only be active in the germinating spore and not in the developing and dormant spore. Alternatively, the maintenance of dormancy could be attributed to the inactivation of phosphoglycerate phosphomutase. As noted in Section 62.1.3.3.4, the inactivity of the enzyme could be due to low levels of Mn^{2+}.[198] This is supported by the observation that the treatment of dormant spores with Mn^{2+} and the ionophore X-537A results in the depletion of accumulated PGA, presumably through the activation of phosphoglycerate phosphomutase by the appearance of Mn^{2+} inside the store. Manganese in vegetative cells exchanges rapidly with extracellular Mn^{2+} in the presence of ionophore X-53A. This is not the case with manganese in forespores, suggesting as noted earlier[197] that the Mn^{2+} is present in a crystalline lattice which results in very low levels of Mn^{2+} and inactive phosphoglycerate phosphomutase.

62.1.3.7 Magnesium and Manganese in Photosynthesis

Light provides the energy for the production of ATP and for the generation of reducing power in photosynthetic organisms. These in turn drive the reduction of CO_2 to give carbohydrates. Photosynthesis also leads to the production of dioxygen from water, except in the cases of green bacteria and purple bacteria.[364]

The photosynthetic apparatus is found in and on membrane structures, which, in plant cells and algae, are located in chloroplasts and are called thylakoids. In bacteria the photosynthetic membrane is derived by complex invagination of the cytoplasmic membrane. The photosynthetic apparatus is made up of antennae, which contain 'light-harvesting' pigment molecules (usually chlorophylls or bacteriochlorophylls) and photochemical reaction centres, which also contain pigments, together with the necessary enzymes and coenzymes.

Photons are absorbed by an array of light-harvesting pigments on the antennae (which may be extrinsic membrane structures). This role is taken by a number of chemically distinct chlorophylls and bacteriochlorophylls, while other pigments such as the carotenoids are also important.[365] A light-harvesting molecule such as chlorophyll will absorb energy and be raised to an excited state. It will then relax to the lowest excited state and transfer this excitation energy directly to another chlorophyll molecule. The energy is passed through a chain of molecules in this way until it reaches the photochemical reaction centre in the membrane. There a chlorophyll or bacteriochlorophyll molecule is excited, and an electron transferred to a primary electron acceptor, A, with the generation of Chl^+ and A^-. The electron is then transferred rapidly from A^- to secondary

acceptors, so that electron transfer occurs in one direction across the membrane with proton transfer in the opposite direction.[366] The resulting potential drives the membrane-bound ATP synthase to give ATP.[367] The electron flow may be cyclic, when Chl^+ is ultimately reduced by the electron, or non-cyclic, when the electron is captured by another acceptor. In this latter case, Chl^+ is reduced by an electron from an external donor, such as water in photosystem II of green plants. The water is thus oxidized to O_2.

In anoxygenic photosynthesis there is no production of O_2. Anoxygenic photosynthesis occurs in green and purple bacteria, which utilize bacteriochlorophylls (Bchl) as reaction centre pigments. The green bacteria have up to 2000 molecules of light-harvesting bacteriochlorophyll per reaction centre, while those of the purple bacteria have about 60. These bacteria use H_2S or organic compounds as hydrogen donors, rather than water.

Certain bacteria such as *Halobacterium halobium* are unique in having no chlorophyll pigments for photosynthesis. Purple patches appear on their cytoplasmic membrane when the organism is grown in strong light. The purple colour is due to the pigment bacteriorhodopsin, which mediates a light-dependent formation of ATP.

The reaction centre pigments in the cyanobacteria (blue-green algae), the prochlorophytes and all photosynthetic eukaryotes are chlorophylls. There are two types of reaction centre in organisms carrying out oxygenic photosynthesis, namely photosystems I and II.[368,369] The primary electron donors of photosystems I and II are designated P700 and P680 respectively. Photosystems I and II respond to light of different wavelength. Each reaction centre has about 200–300 light-harvesting chlorophylls associated with it.

Photosystems I and II operate in concert. Their interaction is described in the 'Z scheme' (shown in outline in Figure 18). In photosystem II, the primary oxidant is able to remove electrons from water. These electrons are transported to photosystem I *via* plastoquinone and plastocyanin to replace PSI electrons that have been used in the reduction of iron–sulfur proteins and transferred *via* NADP to CO_2. Electron flow between PSII and PSI is accompanied by the synthesis of ATP.[367] These oxidizing and reducing aspects of photosynthesis can be separated and other substrates incorporated.

The structure of the reaction centre complexes appears to be well conserved in organisms carrying out oxygen-evolving photosynthesis. In contrast, the organization of antenna complexes seems to be more varied.

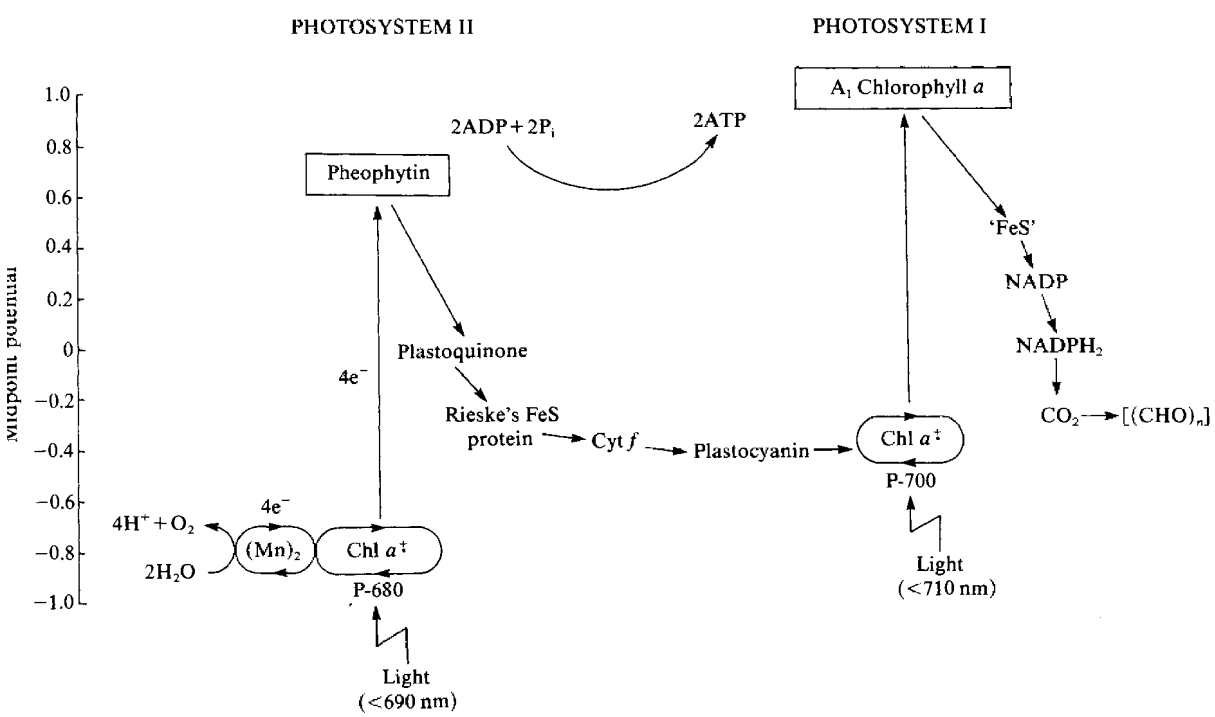


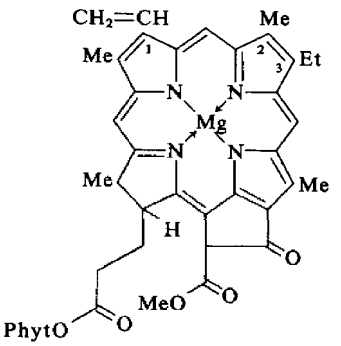
Figure 18 The 'Z scheme' in photosynthesis

While the following discussion centres on the Mg^{2+}-containing pigments, it should be noted that there are two additional major categories of non-chlorophyll-type pigments — the carotenoids and the phycobilins. The latter compounds are open-chain tetrapyrroles.

A manganese protein appears to be involved in the dioxygen-producing reaction in photosystem II.

62.1.3.7.1 Chlorophyll

Chlorophyll is a magnesium tetrapyrrole of the chlorin class that has a unique alicyclic ring. Figure 19 shows the structure of chlorophyll, together with parts of the structure of chlorophyll *b* and bacteriochlorophyll *a*. The fifth and sixth coordination positions may be filled by solvent water, and also offer the possibility of dimer or higher aggregate formation.



Chlorophyll *b*: CHO at position 2
Bacteriochorophyll *a*: COMe at position 1,
Bacteriochlorophyll *b*: COMe at position 1,
CH=CHMe at position 3

Figure 19 The structure of chlorophyll

The structure, function and organization of chlorophyll are well reviewed.[370-372] At one time chlorophyll was thought to be present as *a* or *b*, *b* having a formyl group present at position 3 rather than a methyl group. However, chlorophylls *c*, *d*, c_1 and c_2 are now known. The last two examples involve porphyrins rather than chlorins.

When thylakoid membranes are treated with detergents, much of the chlorophyll released is associated with polypeptides. Studies on membranes from mutant species known to be deficient in some feature of the photochemical apparatus have allowed these to be identified. PSI, PSII and light-harvesting chlorophyll *a*/*b* bound to protein have all been isolated. These can usually be separated into a number of components.

Reaction centres P680 and P700 are thought to involve protein-bound hydrated chlorophyll *a* dimers. Excitation and charge separation give the radical cation species $P680^+$ and $P700^+$. Porphyrin radical cations are well known. Highly conjugated tetrapyrroles with extended π-systems are well suited to participate in this process. It is less easy to see what the role of magnesium might be.[373]

62.1.3.7.2 The manganese protein of photosystem II

Much effort has been put into the isolation, purification and reconstitution of both photosystems. Work on PSII has been concerned especially with the nature of the dioxygen-evolving site, which is thought to be a manganese protein. ESR studies on spinach chloroplasts have led to the postulate of the involvement in oxygen evolution of a pair (or possibly a tetramer) of antiferromagnetically coupled manganese ions present as Mn^{III} and Mn^{IV} during the cycle.[374] Stoichiometries of four Mn and two Mn per molecule of protein have been suggested,[375] but it is probable that only two are required at the reaction centre, and that there is a requirement for two additional divalent cations. These could well be involved in the control of protein conformations to ensure correct interactions between the manganese protein and the other components of the PSII centre.[376]

Progress has been made on purifying the components of PSII, particularly for cyanobacteria and spinach chloroplasts. The presence of Ca^{2+} in the cell-breaking system results in enhanced activity on reconstitution, and it may well be that one of the proteins found is a calcium-binding protein, as supported by the inhibitory effect of the calmodulin antagonist chlorpromazine on activity.[377]

Proteins of molecular weight about 33 000, 24 000 and 16 000 have been isolated from spinach chloroplasts with total inactivation of dioxygen evolution from the particles. Adding back of these proteins to the extracted particles resulted in considerable uptake of the 33 000 molecular weight protein, with associated restoration of O_2-evolving activity.[378] Work with mutant algae also indicates that the manganese protein could have a molecular weight of about 34 000.[379] Such a protein had been isolated by several groups of workers,[380,381] but did not contain manganese, which had been lost during the isolation procedure.[382] However, the native protein has now been released from thylakoids by subjecting chloroplasts to osmotic shock. It has been confirmed that the protein contains two manganese ions in a binuclear site, either $Mn_2^{II,III}$ or $Mn_2^{III,III}$.[383]

Other studies have shown that the 16 000 molecular weight protein is attached to the membrane *via* the 23 000 molecular weight protein, which also binds a manganese protein. However, it is uncertain whether this manganese protein contains the water oxidation site or whether it has a regulatory role which involves maintaining Mn on the membrane. If the latter suggestion is correct, then the water oxidation site could be an intrinsic 34 000 molecular weight protein. Both structural representations are given in Figure 20, but it should be emphasized that these arrangements are still speculative.

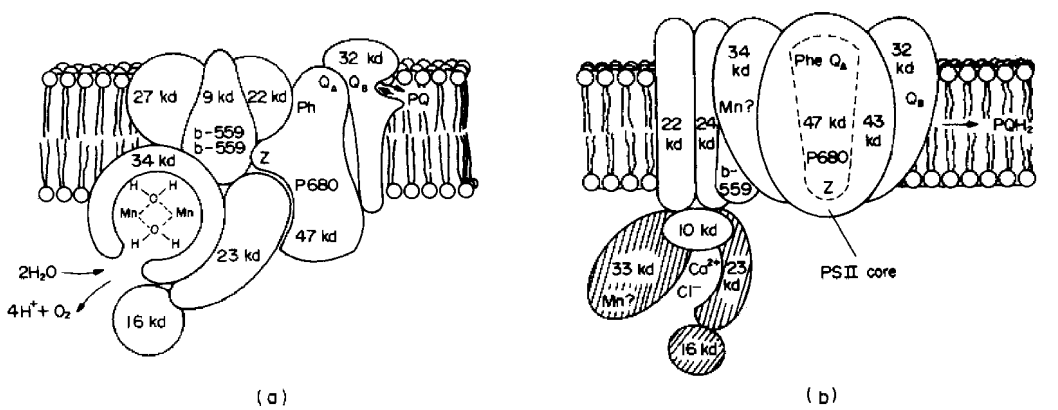


Figure 20 The structure of the photosystem II centre [reproduced (a) with permission from *Trends Biochem. Sci.*, 1984, **9**, 79, and (b) by permission of Professor J. Barber]

The mechanism of dioxygen evolution is still unclear.[384] It seems appropriate to have two water molecules bound to the dimeric manganese centre, for ready formation of an O—O bond. The reaction involves the loss of four electrons, and the possibility therefore of changes of two in the oxidation state of the manganese. However, while it is known that the reaction centre of PSII goes through four consecutive changes in oxidation state before O_2 evolution occurs, it is still unclear if there are changes in the oxidation state of manganese.

EXAFS measurements[385] on manganese in chloroplasts indicated that it is surrounded by C, N or O atoms at distances of approximately 1.8 and 2.15 Å and that another metal, possibly manganese, is 2.7 Å away. This is consistent with a dimeric centre. X-ray absorption edge spectroscopy indicates an average oxidation state of manganese of between Mn^{II} and Mn^{III}.[386] There is other evidence for the involvement of Mn^{III}.[387]

It seems reasonable that the pathway for production of dioxygen would involve the formation of a bridged peroxide and superoxide. Oxidation could involve transient formation of Mn^{III}. Various mechanisms have been put forward[387] and reviewed.[379,384]

62.1.3.7.3 Reaction centres of photosynthetic bacteria

The reaction centres from the photosynthetic purple bacteria are amongst the best characterized. Each reaction centre contains four bacteriochlorophyll molecules, two bacteriophenophytin

molecules (a derivative of bacteriochlorophyll having no Mg^{2+}), one iron–quinone complex and an additional quinone, together with three protein subunits. In some cases they also contain cytochromes. The reaction centre from *Rhodopseudomonas viridis*, which contains bacteriochlorophyll *b*, has been crystallized.[388] The crystal appears to contain two molecules of the reaction centre. This offers the promise of high resolution structural analysis.

The bacteriochlorophyll *a* protein from the green photosynthetic bacterium *Prosthecochloris aestuarii* has been determined at 2.8 Å resolution.[389] It is made up of three identical subunits, tightly packed around a three-fold symmetry axis. Each subunit consists of a core of seven bacteriochlorophyll *a* molecules enclosed within a 'bag' of protein. There are extensive contacts between the phytyl chains of the seven bacteriochlorophylls within each subunit. These tails form an inner hydrophobic core. The seven magnesiums appear to be five-coordinate. In five cases the fifth ligand is a histidine side-chain, in one case a protein backbone carbonyl oxygen, and in the other case a water molecule. It appears that the removal of one or more of the bacteriochlorophyll molecules would destabilize the protein. It is unlikely that the chlorophyll can be reversibly removed from the protein.

62.1.3.8 Calcium as an Enzyme Activator and in Control Processes

Extracellular functions of calcium are better understood than intracellular functions, partly because of the difficulties associated with the analysis of calcium inside the cell. Extracellular roles are those of (a) trigger, (b) an activator and stabilizer of extracellular enzymes, and (c) in bone and teeth (Section 62.1.3.9). Intracellular activities are mainly trigger effects, and are intimately associated with problems of transport and binding.

62.1.3.8.1 The role of calcium in blood coagulation and in protein C, an anticoagulant

Coagulation of blood involves a cascade process, in which there is a sequential activation of zymogens to their active enzymatic forms. Calcium is an essential cofactor in the activation of vitamin K-dependent blood coagulation zymogens prothrombin, and factors VII, IX and X. It is also involved in the activation of protein C, the zymogen of a vitamin K-dependent anticoagulant protease. It has been thought that γ-carboxyglutamate residues were exclusively responsible for the high affinity binding sites for calcium on these proteins. This theory now seems untenable in that modified forms of protein C,[390,391] factor IX[392] and factor X[393] lacking the γ-carboxyglutamate region still have high affinity sites for calcium. The binding of Ca^{2+} to this site in protein C, for example, was found to initiate the conformational change in both the intact and the 'gla'-domainless protein C that was required for activity.[391] There are remarkable sequence homologies in the vitamin K-dependent proteins which suggest that a high affinity 'gla'-independent Ca-binding site may be a common factor.

Prothrombin is the most abundant and best studied of the blood coagulation proteins. It is proteolytically cleaved to give thrombin by activated factor X (a serine protease) in a reaction that also requires activated factor V, a phospholipid and Ca^{2+}. Prothrombin has from six to 15 binding sites[260] for calcium, probably in two classes, but all of low affinity. Binding of calcium causes a conformational change that has been demonstrated by a range of techniques. Fragment 1 of prothrombin consists of the N-terminal 156 amino acids, including all 10 γ-carboxyglutamate residues, and has been used as a model for metal binding to prothrombin. It shows the metal-dependent conformational change. Immunological methods indicate that this change is localized in the 'gla'-rich region of prothrombin (residues 1–42).[394] Low resolution X-ray diffraction studies suggest that the NH_2-terminal one third of fragment 1 is a separate structural domain.[395] A fragment 12–44 is also available, and contains eight 'gla' residues and an internal disulfide loop. This fragment has one high affinity site and four to six lower affinity sites for Gd^{3+}.[396] Reduction of the disulfide group results in loss of the high affinity site, presumably because the —S—S— link plays an important role in controlling the protein geometry. It has been proposed that this high affinity site involves Gla-15 and Gla-26 as ligands.

Binding of cation to fragment 1 also induces dimerization probably by intermolecular bridging of gla residues.[397] Ca^{2+} is the most effective cation in inducing dimerization and Mg^{2+} inhibits. This is in accord with earlier comments on the ability of these two cations to play bridging roles.

The conformational change produced in prothrombin on binding of Ca^{2+} may expose a site that is required for binding to membrane. This may involve the bridging by Ca^{2+} of gla residues in prothrombin to phosphate groups of the phospholipids.[398]

Factors IX and X and protein C have a number of similarities. The γ-carboxyglutamate residues (12, 12 and 11 respectively) are contained in the first 45 or so residues of the N-terminal region of the light chain in protein C and factor X, and in the single polypeptide chain of factor IX. In all three cases, limited proteolysis results in the loss of the gla domain. The remaining fragment still has a high affinity site for Ca^{2+}. All three proteins contain the novel residue β-hydroxyaspartic acid[399] at equivalent positions. This appears to be involved in binding Ca^{2+}. Binding of Ca^{2+} to bovine protein C[400] in the normal protein and in the protein missing the gla domain gives rise to the conformational change necessary for activation of protein C by the thrombin–thrombomodulin complex. Thrombomodulin is a cell surface protein. Thus this non-gla site for Ca^{2+} appears to have an essential role in the case of protein C. Such a role for the equivalent sites in factors IX and X is not yet proven.

Factor X consists of two polypeptides: a light chain of 140 residues which contains 12 gla residues in the N-terminus (residues 1–44) and a heavy chain of 307 residues which contains the serine protease. Factor X is activated to factor Xa by cleavage of an arginyl–isoleucyl link in the heavy chain, either by factor VIIa or factor IXa. Binding of calcium to factor X involves two or three high affinity sites and a large number of low affinity sites.[260] The high affinity sites are usually thought to involve gla residues and to depend upon the presence of disulfide links to give an appropriate tertiary structure. Binding of Ca^{2+} brings about a conformational change followed by binding to phospholipid.

Factor IX is activated by factor XIa by cleavage of the Arg-146 and Arg-147 link to give factor IXa, and by further cleavage between Arg-181 and Val-182 in a metal-dependent reaction to give factor IXa,β. All forms of factor IX have two classes of calcium-binding site. A protease from the venom of *Vipera russelli* is a coagulant, and activates both factors X and IX. This process requires divalent cations but is relatively non-selective.

Factor VII is a single chain protein, which contains gla residues and shows N-terminal sequence homology with the other vitamin K-dependent blood proteins. Binding of Ca^{2+} triggers a conformational change which facilitates interaction with phospholipid.[401]

Protein C functions as an anticoagulant by proteolytically inactivating two protein cofactors of blood coagulation, factors V and VIII.[402] It too circulates in a zymogen form and is activated by limited proteolysis. Protein C appears to contain about 16 sites for Ca^{2+}, all of equal affinity, while activated protein C binds about nine Ca^{2+}. Conformational rearrangement during activation results in loss of binding sites.

62.1.3.8.2 Calcium as an activator of extracellular enzymes

A relatively small number of extracellular enzymes require calcium for activity, although usually not for a catalytic role (Table 11). These enzymes catalyze hydrolysis of various substrates, and show considerable specificity for calcium over magnesium. The proteins are synthesized in the cell where $[Mg^{2+}]/[Ca^{2+}] \approx 10^5$. A dangerous situation would result if magnesium could activate these enzymes inside the cell, and so they must have a very specific requirement for calcium. A further defence against premature activation comes from the fact that these enzymes are synthesized as proenzymes, which require activation by Ca^{2+} to give the enzyme. Trypsin provides a good example. It is synthesized as the proenzyme, trypsinogen. Binding of Ca^{2+} to trypsinogen results

Table 11 Ca^{2+}-dependent Enzymes

Enzyme	*Function*
Phospholipase A_2	Hydrolysis of phospholipids
Thermolysin	Hydrolysis of peptides ($+Zn^{2+}$)
Trypsin	Hydrolysis of peptides
α-Amylase	Hydrolysis of glucosides ($+Zn^{2+}$)
Neutral protease	Hydrolysis of peptides
Acid protease	Digestion of proteoglycan
Staphylococcus nuclease	Hydrolysis of nucleic acids, Ca^{2+} at active site[403]
Subtilisin Carlsberg	

in the unfolding of the protein, with hydrolytic cleavage of a fragment to give trypsin. Further enzymatic digestion of trypsin is prevented by binding Ca^{2+} at a second site, which probably involves bidentate coordination of the carboxylates of Glu-70 and Glu-80 and coordination of the peptide carbonyl groups of Asn-72 and Val-75. Structures of some Ca^{2+} enzymes are given in Table 6.

The ability of Ca^{2+} to crosslink groups and so stabilize proteins against thermal denaturation or hydrolytic attack is well illustrated by thermolysin, which involves four Ca^{2+} and a catalytic Zn^{2+}. The function of the calcium is to stabilize the protein structure.[404] Calcium also protects surface protein of the neural retina from tryptic cleavage.[405]

Latent forms of a neutral protease and an acid protease (pH optimum 5.3) from cartilage are activated by trypsin hydrolysis to give Ca^{2+}-dependent enzymes that catalyze the hydrolysis of proteoglycan.[406] Some Ca^{2+}-dependent proteinases are isolated as proenzymes that can be converted to the active form by high $[Ca^{2+}]$ or by low $[Ca^{2+}]$ in the presence of a digestable substrate.[407]

Phospholipase A_2 catalyzes the hydrolysis of the 2-acyl linkage of all phospholipids. It is secreted as a zymogen by the pancreas, and converted to the active enzyme *via* a specific tryptic cleavage of the Arg-Ala link which removes an N-terminal heptapeptide from the proenzyme. Phospholipase A_2 is one example of the way in which the metabolism of phospholipids is sensitive to calcium at several key points.

The crystal structure of bovine pancreatic phospholipase A_2 has been determined at 1.7 Å resolution.[408] The calcium is bound by a carboxylate group (Asp-49) and three backbone carbonyl groups (Tyr-28, Gly-30 and Gly-32). There was no evidence for a second, weaker binding site for calcium ions.[409] However, the use of ^{43}Ca NMR techniques[410] has confirmed the presence of two cation-binding sites for Ca^{2+}, with $K_1 = 4 \times 10^3$ dm^3 mol^{-1} and $K_2 = 20$ dm^3 mol^{-1}. The strong site was found to be sensitive to a group having a pK_a value of 6.5 and the weak site to a pK_a of 4.5. Evidence had been produced earlier for specific modification of His-48 which inactivated the enzyme.[411] Protonation of histidine is thought to control binding at the strong site even though it is not a ligand to calcium.

Phospholipase A_2 provides a very different site for Ca^{2+} from that in parvalbumin. The rate of calcium exchange is also very different from that found for calcium-binding regulatory proteins. In the latter case, the on-rate for calcium binding is essentially diffusion controlled. For phospholipase A_2, the on-rate is about 100 times less. These differences must be reflected in the different biological roles of the proteins. The binding of Ca^{2+} to calmodulin or troponin C has a regulatory function, and must therefore be rapid. For extracellular enzymes there is no need for such fast exchange rates.

Phospholipase A_2 has an important role in the production of arachidonic acid. This is the precursor of some very important signal molecules such as the prostaglandins, prostacyclins, thromboxanes and leukotrienes. Most of the arachidonic acid in cells is attached at the 2-position of certain phospholipids, and is released by the action of phospholipase A_2. The role of Ca^{2+} in the secretion of these signal molecules will be discussed in the next section.

62.1.3.8.3 Calcium as a trigger

Calcium regulates many cellular functions, either by influx from extracellular sources or by release from intracellular stores. The important role of calcium-binding regulatory proteins such as calmodulin in these processes has been emphasized. Another question of deep fundamental interest is concerned with the way in which the binding of hormones and neurotransmitters at the cell surface can bring about the release of Ca^{2+} from intracellular compartments, with the resulting manifestation of the physiological effects of these hormones *etc.* Clearly chemical messengers must be utilized.

Our understanding of the details of these processes will probably increase in the near future, due to the development of better techniques for the determination of intracellular $[Ca^{2+}]$. One example involves the use of the fluorescent indicator quin 2. This allows quantitative determination of $[Ca^{2+}]$ rather than the mere confirmation of increase or decrease in $[Ca^{2+}]$.[412,413] Quin 2 binds Ca^{2+} with high selectivity, and its fluorescence increases more than four-fold upon saturation with Ca^{2+}. The indicator is added in a lipophilic form, the tetraacetoxymethyl ester, which is taken up by cells. Hydrolysis within the cells gives quin 2, which will then remain in the cell cytosol without binding to cytoplasmic proteins or uptake into organelles. An example of its use lies in the demonstration that release of insulin was mediated by increase in cytosolic Ca^{2+} produced by use of the Ca^{2+}-ionophore ionomycin.[414]

The release of Ca^{2+} as a result of hormone binding to the cell surface seems to be linked to the metabolism of specific phospholipids in the cell membrane. The hydrolysis of phosphatidylinositol is an early event associated with the activation of a wide range of receptor sites, all of which seem to use calcium as one of their intracellular signals.[415] As noted in Section 62.1.3.8.2, this hydrolysis reaction results in the release of arachidonic acid from the 2-position. The head group, inositol, has free hydroxyl groups which can be phosphorylated to give polyphosphoinositides that appear to be particularly important in calcium metabolism. One example involves the stimulation of hepatocytes by vasoactive peptides or α_1 adrenergic agonists. This results in mobilization of intracellular calcium, and also the breakdown of phosphatidylinositol 4,5-diphosphate to release *myo*-inositol 1,4,5-triphosphate.[416] This compound will release Ca^{2+} from non-mitochondrial, vesicular stores in other experiments, and so could well be a second messenger for the hormonal mobilization of Ca^{2+} in liver.

The release of Ca^{2+} in response to such second messengers is known to activate the phosphorylation of a range of cytosolic proteins by Ca^{2+}-dependent protein kinases, for example in hepatocytes,[417] adrenal cortex[418] and other cells.[419] Ca^{2+} inhibits cAMP-activated protein kinase in parathyroid glands.[420] Phosphorylation of proteins produced in the pancreatic β-cell in response to enhanced $[Ca^{2+}]$ may involve calmodulin, while the stimulus produced by glucose is potentiated by cAMP.[421] A calmodulin-activated NAD kinase is present in the outer mitochondrial membrane of corn.[422]

The secretion of neurotransmitters from synaptic vesicles at neuroterminals requires entry of Ca^{2+} into the nerve terminal. Calmodulin is also involved,[423] and calcium-dependent[424] and calcium-independent[425] sites for calmodulin have been found on cholinergic synaptic vesicles from the electric organ of *Narcine brasiliensis*. Again it appears that phosphorylation of a protein is required.

Secretory material (hormones, neurotransmitters, control and defence molecules) is stored in vesicles or granules. After an appropriate stimulus these granules migrate to the periphery of the cell and are extruded in the process of exocytosis. Calcium appears to be involved in these processes, and may bind to the granules and facilitate fusion with the cell membrane by bridging negatively charged groups. In addition, at least for chromaffin granules, aggregation is also assisted by the protein synexin.[426]

It is of interest to consider examples of trigger effects of Ca^{2+} in addition to those given above. Calcium has key roles in the activation of spermatozoa and the fertilization of eggs.[428] A striking example of the use of the photoprotein aequorin involves the measurement of free Ca^{2+} in the eggs of a freshwater fish, the medaka. On activation by spermatozoa, the emission of light from the aequorin-injected eggs increases 10 000-fold. Entry of the sperm triggers a calcium wave that is released from internal sites and reaches the opposite side within two minutes.[429]

The trigger function of calcium ions in microbes is remarkably interesting. *Paramecium* is able to reverse its direction of travel on encountering some obstacle.[430] An influx of Ca^{2+} into the cilia, running down a concentration gradient through a calcium channel results in a change in ciliary beating, and hence in the direction of swimming. It then resumes its previous forward motion, once the calcium has been pumped out (50 ms). Mutant species in which Ca^{2+} influx cannot occur are unable to reverse. Organisms whose outer membranes have been disrupted swim forward when $[Ca^{2+}]$ is in the range 10^{-7}–10^{-8} mol dm^{-3}, and in reverse at higher $[Ca^{2+}]$. The target of the incoming Ca^{2+} is a membrane-bound guanylate cyclase which also requires calmodulin.[431] A Ca^{2+}-dependent ATPase is also present in the cilia.[432]

Similarly, chemotactic behaviour of bacteria is controlled by Ca^{2+}. Mobile bacteria swim towards certain chemicals and away from others. Such bacteria can swim smoothly in a straight line or tumble, which results in random changes in direction. When heading towards repellents bacteria tumble more frequently to increase the probability of swimming away. Influx of Ca^{2+} causes tumbling. Such behaviour has been found for *Bacillus subtilis*,[433] but apparently not for *E. coli*.[434] Calcium accelerates the swimming speed of *Chlamydomonas reinhardii*[435] and regulates reverse motion in phototactically active *Phormidium uncinatum* and *Halobacterium halobium*.[436,437] Phototaxis in *H. halobium* involves a methylation–demethylation process which is calcium dependent.[438] Attractant stimuli raise the level of methylation of membrane proteins, while repellent stimuli cause demethylation and the enhanced opportunity for reversal of direction. Ca^{2+} deactivates the methyl transferase and activates a methyl esterase.[439]

The role of calcium in cell division is controversial. The measurement of cation fluxes in synchronized cultures of *Tetrahymena* shows an influx of calcium 30 minutes prior to the initiation of cell division.[440] However, there is also an influx of magnesium, and it has been suggested[441] that the fluctuation of these metals during the synchronized division cycle is an effect rather than a cause.

Cyclic uptake and release of Ca^{2+} from the extracellular medium occur during mitosis in *Physarum polycephalum*, and correlate with specific structural and kinetic events in the mitotic nuclei.[442] The membrane system in the mitotic apparatus in *Haemanthus* endosperm cells functions in the localized release of Ca^{2+}, so regulating the events of mitosis.[443] It is known that calcium exerts effects on the stability of spindle microtubules. An alternative view is that free magnesium concentration acts as the fundamental regulator of the cell cycle.[444] Tubulin polymerization depends on the presence of magnesium and the absence of calcium, and control of the Ca^{2+}/Mg^{2+} ratio is relevant to spindle assembly.

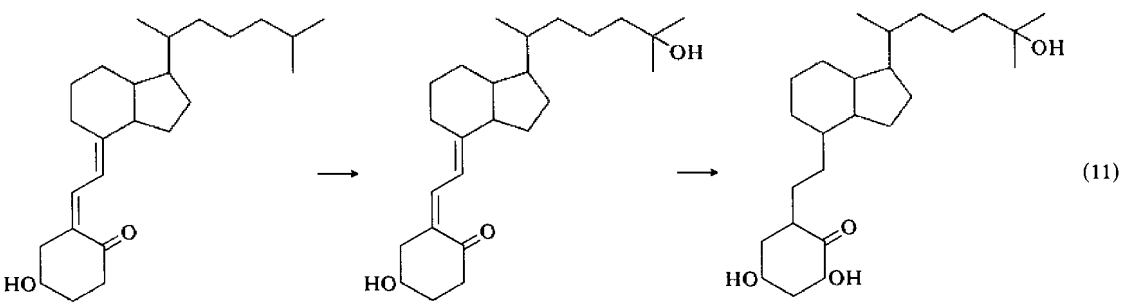
Calcium is necessary for cell division in *Lactobacillus bifidus*,[445] and for the transition of *L. bulgaricus*[446] from long filamentous chains to short bacilloid rods.

62.1.3.9 Calcification and Mobilization

The controlled deposition of calcium salts is essential for the development of extracellular structures such as bones, teeth and shell. The process begins with uptake of calcium in the intestine, followed by transport, and then the laying down of structures. A complex system is necessary for the control of all these stages, and involves, for example, vitamin D, parathyroid hormone, calcium-binding proteins for transport, and a range of other proteins and polysaccharides for ordered deposition. Precipitation of calcium salts in the incorrect location can result in stone formation, osteoarthritis, cataracts and arterial disorders.

62.1.3.9.1 Uptake of calcium from the intestine

Uptake of Ca^{2+} from the intestine is stimulated by vitamin D.[447] Vitamin D_3 is converted to the 25-hydroxy derivative in the liver (equation 11) by a two component mixed-function hydroxylase.[448] The metabolically active 1,25-dihydroxy form is synthesized by further hydroxylation in the kidney. This latter stage involves the renal 25-hydroxyvitamin D_3-1-hydroxylase in a reaction which is controlled by Ca^{2+}, parathyroid hormone and phosphate. This renal hydroxylase contains a flavoprotein, an iron-sulfur protein (with an Fe_2S_2 cluster) and cytochrome P-450.[447]



(11)

Vitamin D_3 25-(OH)D_3 1,25-(OH)$_2D_3$

The next stage involves the synthesis of specific calcium-binding proteins, typified by the intestinal CaBP[253] discussed in Section 62.1.3.4.5, which probably stimulates the transport of calcium. The role of the protein in vitamin D-dependent absorption of calcium is supported by the good correlation between the concentration of CaBP and the rate of calcium absorption. Under conditions of low calcium or phosphorus diets, chicks and other animals produce more intestinal CaBP to increase the efficiency of uptake of calcium. In general, adaptation to a low calcium diet involves increased synthesis of 1,25-$(OH)_2D_3$ and the intestinal CaBP. Lowered requirements for calcium in old age are manifested by lower levels of both factors.[449,450]

Advances have been made in the localization of the cellular sites of 1,25-$(OH)_2D_3$ in target tissue. Receptor proteins have been extracted, and, in the case of the chick intestinal receptor, purified to homogeneity.[451] The ability of 1,25-$(OH)_2D_3$ to stimulate absorption of calcium is blocked reversibly by inhibitors of RNA and protein synthesis. This suggests that 1,25-$(OH)_2D_3$ functions by a nuclear mechanism.

The transfer of phosphate is stimulated by 1,25-$(OH)_2D_3$, but little is known about the mechanism. Vitamin D also stimulates the activities of alkaline phosphatase and Ca^{2+}-ATPase. This may be involved in the supply of inorganic phosphate.

$1,25\text{-}(OH)_2D_3$ also appears to mobilize calcium from bone, although the presence of parathyroid hormone is necessary. The rise in plasma calcium produced by $1,25\text{-}(OH)_2D_3$ also seems to involve protein and RNA synthesis, and it has been suggested that a calcium-binding protein is synthesized in response to the vitamin D.[452] High affinity binding proteins for vitamin D metabolites have been found in bone cytosols.

Hypercalcaemia and soft-tissue calcification have been found in animals grazing on plants such as *Cestrum diurnum* and *Solanum malacoxylon*, and attributed to the presence of a $1,25\text{-}(OH)_2D_3$-glycoside.[453] The calcinogenic plant *Trisetum flavescens* causes severe calcification on ingestion, but the vitamin D_3 species responsible has not been identified.[454]

62.1.3.9.2 Deposition of calcium

The calcium taken up by living systems will be found mainly as extracellular deposits or structures, with a small amount present in intracellular stores, together with some in various extracellular fluids. The calcium in fluids will be bound to protein or will be 'free' in solution, with a few percent bound to small molecules or anions. The calcium in solution will exchange with the calcium in structures such as bone and teeth, due to the activity of hormones such as $1,25\text{-}(OH)_2D_3$, parathyroid hormone and calcitonin,[455] which are responsible for the remodelling and repair of bone.

The level of calcium in solution will depend upon the presence of precipitating anions, notably phosphate and carbonate. Calcium will precipitate as the phosphate to give hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, in bones and teeth, and as the phosphate or carbonate to give other structures, including small crystals, or non-crystalline deposits in cells. Small crystals of calcium carbonate, found in the inner ear of some animals, are responsible for the control of balance. Various calcified tissues result from the precipitation of calcium salts, such as hydroxyapatite in the calcification of the aortic wall, and the oxalate in various stones.

These processes are all subject to several controls. Precipitation should only occur when required and crystal growth must be controlled. This is brought about by the action of certain proteins which control nucleation and the direction of crystal growth. Polysaccharides are involved in the control of the growth of calcium carbonate crystals in shells and coccoliths. Coccoliths provide a remarkable example of mineralized structures formed inside the cell. They are structures of extraordinary complexity containing calcium carbonate as calcite. They are extruded from the cell to form plates on the outer surface. In *Coccolithus huxleyi*, each coccolith is made up of about 30 units of calcite, each of them being a single crystal of complicated shape. The units are passed through the plasma membrane and fit together to form a plate. Each flagellate may contain some 200 coccoliths. Some eight coccoliths are synthesized every hour, representing a remarkable flux of mineral. Coccoliths contain a polysaccharide which binds calcium, and which could act as a matrix in coccolith formation.[456] The Golgi apparatus is responsible for coccolith formation.

The precipitation of calcium phosphate in the development of bone structure is a major topic beyond the scope of this discussion. It should be noted, however, that this process can be controlled by proteins and/or polysaccharides that provide sites for nucleation and that match features in the geometry of the crystal, such as repeat distances between certain groups. Other proteins can inhibit crystal development. Granular deposits of calcium involve small crystals so that deposition and reabsorption will be rapid. The size of the crystals can be controlled by their protein and/or polysaccharide environment, or even by a vesicular membrane which could act as a template.

Two types of protein have been isolated from bone and teeth. Osteocalcin[457] is a gla protein synthesized in bone. Osteocalcin from various sources shows a high degree of sequence homology; the protein from calf and swordfish has gla residues 17, 21 and 24. Human osteocalcin has gla residues 20 and 24, with residue 17 only partially carboxylated, a possible manifestation of age.

Osteocalcin has two high affinity and two or three low affinity sites for calcium.[458] It limits growth of calcium phosphate crystals, and inhibits precipitation of hydroxyapatite. This cannot be achieved by the decarboxylated protein. Calcified tissue from various sources also contains gla proteins.[459] Gla proteins are not found in invertebrates.

A phosphoprotein from teeth assists the nucleation of dentine. This protein has a number of phosphorylated serine residues.[460]

Various smaller molecules and ions can also inhibit the growth of crystals of calcium phosphate such as phosphocitrate, proteoglycans and trimetaphosphate. Other compounds act as accelerators.

The different functions of the gla proteins and phosphoproteins must be related to the packing in hydroxyapatite and apatite [$Ca_2(OH)(PO_4)$], but probably depend too on the relative disposition of the oxygen donors in the gla and phosphoryl groups.

Acidic polypeptides which inhibit the precipitation of calcium oxalate in urine contain gla residues. Other precipitating-inhibiting proteins found in saliva which are rich in tyrosine and proline residues have been discussed in Section 62.1.3.4.8.

62.1.4 THE BIOCHEMISTRY OF ZINC

Zinc is one of the more abundant trace elements (Table 1), and its essential role in biological processes is now well established. Over 100 enzymes require zinc for activity, even though only a relatively small number of these have been well studied. Examples are listed in Table 12. In this discussion most attention will be paid to the well-characterized zinc enzymes, but it must be stressed that there is increasing interest in other aspects of the biological chemistry of zinc, notably

Table 12 Zn^{2+}-dependent Metalloenzymes

Enzyme	*Source*
Oxidoreductases	
Alcohol dehydrogenase	Vertebrates, plants, microbes
D-Lactate cytochrome reductase	*S. cerevisiae*
Superoxide dismutase	Vertebrates, plants, fungi, bacteria
NADH-dependent lactate dehydrogenase	*S. cerevisiae*
D-Glyceraldehyde 3-phosphate dehydrogenase	
Transferases	
Transcarboxylase	*Propionibacterium shermanii*
Aspartate transcarbamalase	*E. coli*
Phosphoglucomutase	
RNA polymerase	*S. cerevisiae*, bacteria
Deoxynucleotidyl transferase	
Reverse transcriptase	
Mercaptopyruvate sulfur transferase	Rat liver, *E. coli*
Hydrolases	
Fructose-1,6-bisphosphatase	Mammals
Alkaline phosphatase	Mammals, bacteria
Phosphodiesterase	Snake venom
Cyclic nucleotide phosphodiesterase	*S. cerevisiae*[1]
Alkaline protease	
α-Amylase	*Penicillium cirtrinum*
α-D-Mannosidase	Jack bean
Phospholipase C	*Bacillus cereus*
Leucine aminopeptidase	Mammals, fungi, bacteria
Carboxypeptidase A	Vertebrates, crustaceans
Carboxypeptidase B	Mammals, crustaceans
Dipeptidase	Mammals, bacteria
Neutral protease	Vertebrates, fungi, bacteria
β-Lactamase II	*B. cereus*
Thermolysin	Thermophilic organisms
Collagenase	Mammals, bacteria
Angiotensin-converting enzyme	Mammals
Elastase	*Pseudomonas aeruginosa*
Aminocyclase	Kidney
AMP deaminase	Rabbit muscle
Lyases	
Aldolase	
L-Rhamnulose-1-phosphate aldolase	*E. coli*
Carbonic anhydrase	Animals, plants
Glyoxalase I	Mammals, *S. cerevisiae*
δ-Aminolevulinic acid dihydratase	Liver, erythrocytes
Isomerases	
Phosphomannose isomerase	*S. cerevisiae*
Ligases	
tRNA synthetase	*E. coli*
Pyruvate carboxylase	*S. cerevisiae*, bacteria

1. J. Londesborough and K. Suoranta, *J. Biol. Chem.*, 1983, **258**, 2966.

nutritional, medicinal and microbial aspects.[461,462,463] Deficiency of zinc produces some remarkable effects: such deficiency is sometimes brought about by dietary or other factors which decrease intestinal absorption.

The role of zinc in the enzymes listed in Table 12 is very often that of a strong Lewis acid, in which substrates are coordinated, polarized and hence activated. In other cases, zinc may play a regulatory, structural or template role. Zinc may also have a structural function in other biological molecules, for example in the unwinding and subsequent rewinding of the double-stranded polymers involved in replication and transcriptional processes. There is also evidence for a role for zinc in the stabilization of membranes and cell walls.[463] The high concentrations of zinc in certain snake venoms reflect the presence in the venom of proteolytic enzymes and hemorrhagic toxins that all require zinc for activity.[464]

A number of general reviews on the biochemistry of zinc are available.[461–472] Some of these cover the important question of analysis,[461,471] while others deal specifically with structural aspects.[467,468] Reviews on specific enzymes will be given as appropriate.

Two types of mechanism have been discussed for many zinc enzymes, particularly in cases where hydrolysis reactions are involved. In the 'zinc carbonyl' mechanism, the substrate is proposed to bind to the zinc through a carbonyl oxygen atom and to undergo polarization, thus enhancing nucleophilic attack on the carbon of the carbonyl group. The mechanism may also hold for other substrate types, such as the phosphate group as in nucleotidyl polymerases. In this mechanism, the substrate displaces the aqua group on the zinc. In the alternative proposal, the 'zinc hydroxide' mechanism, the aqua group is suggested to be deprotonated. The bound hydroxide then attacks the carbon atom of the carbonyl group in peptide substrates, for example, or acts as a proton acceptor as in the case of alcohol dehydrogenase. The function of the Zn^{II} is to lower the pK_a of the bound water to about 7 so that the enzyme exists as a hydroxide species at physiological pH values. In both mechanisms there could well be an additional role for the zinc centre of ordering the conformation of the active site.

Kinetic studies on a variety of model compounds involving the hydrolysis of ligands bound to Co^{III} and other metal centres have shown excellent evidence for the efficiency of the metal-bound hydroxide pathway compared to that involving polarization of bound substrate.[473,474]

More recently mechanistic proposals have included the suggestion that the substrate binds to give a five-coordinate zinc without displacement of the water group.

One of the problems in studying zinc enzymes is that the zinc is 'silent' from both electronic and nuclear points of view, and so provides no information about site symmetry and ligand groups. Accordingly a dominant feature of work on zinc enzymes has been the use of probe metal ions to replace Zn^{2+}. Co^{II} has been used with some success, while a more recent innovation is the use of $^{113}Cd^{2+}$ as a probe, and the application of Cd NMR techniques.

The role of zinc in the RNA polymerases has been discussed in Section 62.1.3.5.7.

62.1.4.1 Transport of Zinc

The mechanisms of accumulation of zinc are still largely unclarified. Some information is available for uptake by bacteria, yeasts and algae.[463] This is energy dependent, and often inhibited by Ca^{2+} and sometimes by Cd^{2+}. Uptake by mitochondria occurs by energy-dependent and -independent pathways, the zinc being precipitated as zinc phosphate. Uptake by tissue culture cells is hormone stimulated,[475] while transport by intestinal cells is dependent upon sodium. In the rat, zinc is absorbed throughout the length of the small intestine but only slightly through the stomach and large intestine. Intestinal absorption of zinc is an energy-dependent process. One manifestation of zinc deficiency in humans is *acrodermatitis enteropathica.* This is treated with diiodohydroxyquinone, which is thought to complex Zn^{2+} to give a complex that is more readily absorbed by intestinal mucosal cells than is zinc alone.[476] It is clear that symptoms of zinc deficiency are sometimes seen in animals and plants because the zinc present in the environment is effectively not available for uptake. Thus, inositol hexaphosphate (phytate) binds zinc and inhibits its uptake by the intestine. It has been proposed that the high incidence of dwarfism in certain countries is due to zinc deficiency brought about by the consumption of cereals and grains containing high levels of phytate.

It is suggested that zinc is stored by metallothioneins in many tissues. These are low molecular weight proteins with a high incidence of cysteine residues. A zinc-binding protein, which is similar to metallothionein, has been isolated from yeasts[477] and the cyanobacterium *Anacystis nidulans.*[478] Zinc uptake in energy-starved *Candida utilis* requires protein synthesis. While it is possible that

this is a zinc permease, it is also possible that intracellular storage molecules have to be available before uptake of zinc can occur.[477] Dietary zinc supplements lead to elevated levels of metallothionein-bound zinc. The metallothionein is rapidly synthesized to serve as a temporary store for the zinc.

62.1.4.2 Carbonic Anhydrase

This enzyme, which occurs in animals, plants and certain microorganisms, is a most effective catalyst of the reversible hydration of CO_2 and dehydration of HCO_3^-.[479-482] It also catalyzes reactions of a number of compounds which undergo hydrolysis or hydration, for example the hydrolysis of 4-nitrophenyl acetate and the hydration of acetaldehyde.[480]

The most studied carbonic anhydrase is the one isolated from bovine or human red blood cells. It contains one zinc per 30 000 molecular weight, and exists as two major isoenzymes, B and C. Each isoenzyme has a distinct amino acid composition with about 60% sequence homology.

Carbonic anhydrase is inhibited by several classes of inhibitor. The sulfonamides, of general formula XSO_2NH_2, are well known, while inhibition by simple anions occurs particularly at higher pH values. Imidazole is a unique example as it is the only compound known at present to act as a competitive inhibitor for the hydration of CO_2. A great deal of mechanistic information has come from a study of the action of these compounds.

62.1.4.2.1 Structural studies

The human isoenzymes B and C, and the bovine B isoenzyme have been studied by X-ray diffraction at high resolution.[483-484] They are ellipsoidal in shape with approximate dimensions $41 \times 42 \times 55$ Å^3. The zinc ion lies near the bottom of a cleft 16 Å deep, which reaches nearly to the centre of the molecule. It is bound by the imidazole groups of three histidine residues, His-94, His-96 and His-119. The fourth coordination site is occupied by a water molecule, giving a distorted tetrahedral geometry. The coordinated water molecule is linked by hydrogen bonding to Thr-199, which in turn is hydrogen bonded to Glu-106. These are about 4 Å away from the zinc ion, close enough for the Glu-106 to play a catalytic role. The active site is represented in Figure 21. The general features of the cleft have been confirmed by the use of a range of spin-labelled sulfonamide inhibitors.[485]

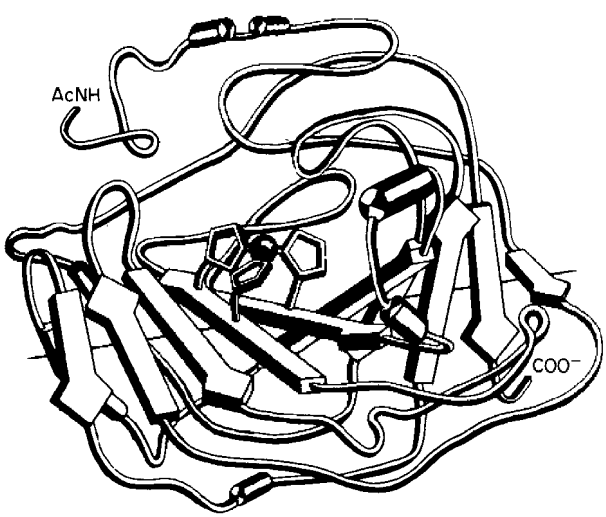


Figure 21 The structure of carbonic anhydrase. Cylinders represent helices, and arrows represent β-structure (reproduced with permission from 'Isozymes I, Molecular Structure', Academic, New York, 1975, p. 575

The structure of the human carbonic anhydrase B–imidazole complex involves five-coordinate zinc, the aqua group being retained.[486] This is an important result in view of the competitive inhibition by imidazole. Sulfonamides displace the aqua ligand, being bound to the zinc by an O or N donor atom, with a second O atom forming an additional long bond to the zinc, making it

effectively five-coordinate.[487] EXAFS measurements have confirmed the direct binding of iodide to zinc in the iodide complex with carbonic anhydrase,[488] while the use of other techniques has demonstrated the binding of Cl^- and Br^- to zinc.

62.1.4.2.2 Kinetics of the carbonic anhydrase-catalyzed reversible hydration of CO_2

The hydration of CO_2 occurs at a relatively slow rate in the absence of a catalyst, with a rate constant of 0.037 s^{-1} at 25 °C (equation 12). The enzyme catalyzes the reaction by a factor of 10^7 at pH 7, the human isoenzyme C being more active than human carbonic anhydrase B by a factor of 30. Bovine B enzyme is also of high activity. The K_m value for binding CO_2 is nearly independent of pH (14 mmol dm^{-3}, for human carbonic anhydrase C), but the rate constant is dependent upon pH. Values of k_{cat} increase with pH, and indicate that a group having a pK_a value of 7.1 is involved in the active site and controls catalytic activity, the deprotonated form being the active species. This group appears to be involved at the metal site, as shown by studies on the cobalt carbonic anhydrase. The *d–d* spectrum is pH dependent, suggesting the existence of two forms of the enzyme, related by a protonation that affects the environment of the cobalt centre. The pH dependence of the *d–d* spectrum gives a pK_a value of 7.1, similar to the value obtained from the kinetic studies.

$$OH^- + CO_2 \overset{k}{\rightleftharpoons} HCO_3^- \tag{12}$$

One complication lies in the fact that that loss of the proton from the enzyme to give the active form could be slower than the observed catalytic rate, as the rate constant for the deprotonation of a weak acid with a pK_a of 7 cannot be greater than 10^3–10^4 s^{-1} if H_2O is the proton acceptor. In fact, proton transfer to solvent is mediated by buffer, so that at low buffer concentrations, proton loss is rate limiting.[489–491] At buffer concentrations greater than 10 mmol dm^{-3} the reaction is no longer rate-limited by buffer-mediated H^+ transfer to solvent. Under these conditions, there are deuterium isotope effects on k_{cat} and K_m of about 3–4, while $K_m^{HCO_3^-}$ is nearly independent of pH. These results have been interpreted[479] in terms of rate-limiting H^+ transfer between the catalytic group and a 'proton-transfer' group, which may be His-64. This will be followed by fast transfer to buffer. Rate-determining transfer of protons between two groups in the enzyme at high buffer concentration is also supported by studies on the exchange of ^{18}O between CO_2 and H_2O and between $^{12}CO_2$ and $^{13}CO_2$ in the presence of human carbonic anhydrase C.[492]

The identity of the group with pK_a = 7.1 which is involved in the active site has been a fertile source of controversy. Candidates for this group have included a histidine residue, a Zn-coordinated imidazole, the carboxyl group of Glu-106 and the aqua group on the Zn^{II}. Chemical modification studies have eliminated His-64, as enzyme activity is maintained. NMR studies suggest that the catalytic group does not involve a histidine residue.[493] The most likely group is the zinc-bound water molecule, first suggested in 1959.[494] Objections to this proposal were based upon the pK_a value of 7.1, which was thought to be impossibly low for an aqua group. Studies on model compounds have shown that this is not the case. Values for pK_a in the range 8.1 to 8.7 have been found for Zn^{II}-bound H_2O in a five-coordinate complex,[495] while a pK of 8.8 has been attributed to ionization of water in aqua[tris(3,5-dimethyl-1-pyrazolyl)methyl]aminecobalt(II) perchlorate.[496] The lowest pK_a value measured so far is probably for water bound to the [tris[(4,5-dimethyl-2-imidazolyl)methyl]phosphine oxide]zinc(II) cation, which has a pK_a of 6.19[497] in 20% ethanol. The hydrophobic environment provided by the enzyme will also contribute to a lowered pK_a value. The effectiveness of metal-bound hydroxide ion has already been discussed.

It should be noted that the kinetics for the human B isoenzyme are more complicated in that the pH dependence indicates that additional groups influence the rate. Studies with the isoenzyme carboxymethylated at His-200 prepared from ^{13}C-labelled bromoacetate show that the pH dependence of the ^{13}C NMR signal can be fitted to a curve with two pK_a values of 6.0 and 9.2, but not to a curve with a single pK_a. The second group could be the imidazole side-chain of His-200. Paramagnetically shifted ^{13}C NMR resonances in the modified Co^{II} human carbonic anhydrase-B have been located by a novel method.[498] This should allow the confirmation of an earlier postulate that the carboxymethyl carboxylate is a ligand for zinc in the modified enzyme.

62.1.4.2.3 Metallocarbonic anhydrases

The zinc can be removed from carbonic anhydrase by dialysis against certain chelating agents, notably pyridine-2,6-dicarboxylic acid.[499] The apoenzyme can be reconstituted by a number of

divalent cations, which occupy the zinc site. The Co^{II} enzyme has about 50% activity, while the Cd^{II} and Mn^{II} enzymes have slight activity. The Hg^{II}, Cu^{II}, Ni^{II} and VO^{2+} enzymes have negligible activity, possibly due to changes in geometry (Hg^{II}), or to kinetic factors. Catalytic activity appears to be related to a group having a pK_a near 7.

Most work has involved the cobalt(II) carbonic anhydrase, and some illustrations will be given. Work with metallocarbonic anhydrases has been reviewed.[482]

The visible spectrum of the Co^{II} carbonic anhydrase varies with pH and with the presence of inhibitory anions due to changes in geometry. Some inhibitor complexes involve tetrahedral geometry, others give five-coordinate stereochemistry and a third group, including the enzyme, have spectra that suggest the presence of both tetrahedral and five-coordinate species. The spectrum of the chloride adduct is temperature dependent, suggesting a thermal equilibrium between four- and five-coordinate species. The high activity bovine B isoenzyme and the low activity human B isoenzyme reveal differences in geometry at pH 5.7. The bovine enzyme is four-coordinate, whereas the human enzyme is largely five-coordinate, due to coordination of a second water molecule.[500]

The *d–d*, CD and MCD spectra of cobalt carbonic anhydrase are pH dependent, as noted earlier. In general the *d–d* and MCD spectra of the enzyme in acidic pH resemble those of Co^{II} complexes of tetrahedral geometry. The spectra at alkaline pH are different from the spectra at acid pH, and suggest the presence of a distorted five-coordinate cobalt(II) centre. Thus it appears that in the active form of the enzyme the metal is present in a five-coordinate geometry.

The measurement of the spin-lattice relaxation of solvent water protons in solutions of Co^{II} carbonic anhydrase leads to the establishment of pK_a values of 6.1 and 8.5. The former value probably refers to the $Co—OH_2$ group, while the latter pK_a is suggested to be due to enzyme-bound bicarbonate.[501]

62.1.4.2.4 Inhibitors for carbonic anhydrase

The ability of zinc in carbonic anhydrase to become five-coordinate is also confirmed by the structural studies on enzyme–inhibitor complexes discussed in Section 62.1.4.2.1. There is much evidence for the coordination of anionic inhibitors to the metal, while the competitive inhibitor imidazole gives a five-coordinate centre. Sulfonamides[481,502] are powerful inhibitors which bind directly to the zinc and also interact with the protein. The sulfonamide acetazolamide has significant affinity for the apoenzyme. It is probable[503] that the first interaction between the enzyme and aromatic sulfonamides is a hydrophobic interaction between the aromatic ring and residues in the active site cavity, followed by ionization of the SO_2NH_2 group prior to complex formation. Sulfonamides only bind to the zinc and cobalt enzymes, *i.e.* the two metals that give an active enzyme.

Several aspects of inhibition by simple anions are under study. The nature of this inhibition appears to be pH dependent. At low pH it is non-competitive (equation 13). It is suggested that increase in pH results in conversion of the aqua group to a hydroxo group with loss of the anion, as the Zn^{II} in the active site appears unable to accommodate two negative charges in its inner sphere. At higher pH a different type of inhibition occurs (uncompetitive),[504] in which the binding of CO_2 to the alkaline form of the enzyme modifies the formal charge on the zinc so that binding of anion is once more allowed (equation 14). This complex is inactive, since release of bicarbonate would turn over the substrate. Therefore, an additional step must precede product release, probably one of the proton-transfer steps described earlier. The presence of the anion must block this step.

$$\geqslant Zn—OH_2 + I^- \rightleftharpoons \geqslant Zn\begin{matrix} I \\ \diagdown \\ OH_2 \end{matrix} \qquad (13)$$

$$\geqslant Zn—OH + CO_2 + I^- \rightleftharpoons \begin{matrix} \diagdown \\ —Zn \\ \diagup \\ H \end{matrix}\begin{matrix} I \\ \diagup \\ O \\ \diagdown \\ O \end{matrix}\begin{matrix} O^{\delta-} \\ \diagup\!\!\diagdown \\ C \\ \diagdown\!\!\diagup \\ O^{\delta-} \end{matrix} \qquad (14)$$

62.1.4.2.5 Mechanism of action of carbonic anhydrase

The discussion of this mechanism is simplified in that the role of the ionizable zinc-bound water molecule as the catalytic group is now fairly generally accepted. The nucleophilic power

of this hydroxo group is much greater than would be expected from its pK_a value. There is also increasing support for the view that the CO_2 is bound weakly at a fifth coordination site. The effect of Co^{II} on the ^{13}C relaxation of $^{13}CO_2$ and $H^{13}CO_3^-$ in the cobalt(II) enzyme has been interpreted in terms of both substrates binding near the metal. A $^{13}C—Co^{II}$ distance of 3.6 Å has been calculated, suggesting that HCO_3^- and perhaps CO_2 are bound to the metal.[505] The competition between imidazole and CO_2 also suggests that CO_2 is bound. Anionic inhibitors will function by displacing OH^-. A scheme is shown (Figure 22), in which it is assumed that the high pH form of the enzyme is five-coordinate, a water molecule being displaced by CO_2.

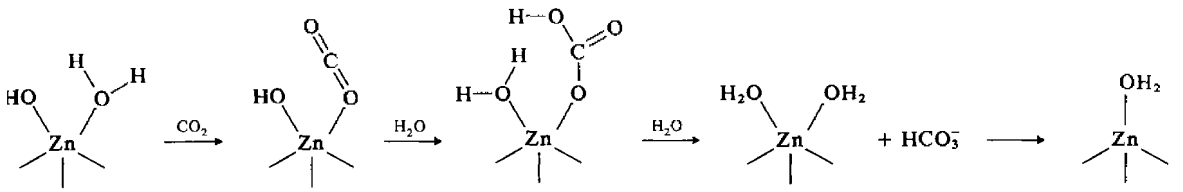


Figure 22 A mechanistic scheme for carbonic anhydrase

62.1.4.3 Carboxypeptidase

The carboxypeptidases are released from their inactive precursors in the pancreatic juice of animals. The most studied example is bovine carboxypeptidase A, which contains one mole of zinc per protein molecular weight of 34 500. These enzymes cleave the C-terminal amino acid residue from peptides and proteins, when the side-chain of the C-terminal residue is aromatic or branched aliphatic of L configuration. At least the first five residues in the substrate affect the activity of the enzyme. The enzyme also shows esterase activity. Esters and peptides inhibit each other competitively, indicating that the peptidase and esterase sites overlap, even if they are not the same.

62.1.4.3.1 Structural studies

Bovine CPA is an ellipsoidal molecule, with dimensions $50 \times 42 \times 38$ Å^3.[506,507] The zinc is bound in a cleft by three protein residues, two imidazoles and a bidentate carboxyl group of His-69, His-196 and Glu-72. The remaining position is filled by a water molecule to give a five-coordinate environment around the zinc. A number of other residues appear to be involved in the active site, namely Glu-270, Tyr-248 and Arg-145. These have detailed roles in mechanisms put forward on the basis of the crystallographic data on a stable enzyme–substrate complex with the dipeptide glycyl-L-tyrosine. This complex is isomorphous with the enzyme, so allowing the clarification of the binding of the substrate. The C-terminal side chain of the substrate fits into a pocket that contains no specific binding groups, in accord with the lack of high specificity for the nature of the side-chain, but is large enough to accommodate bulky substituents. The free carboxylate group interacts with the positively charged guanidinium group of Arg-145, while the carboxyl oxygen of the CONH group undergoing attack is probably coordinated to the zinc with displacement of the water molecule.

Figure 23 shows the conformational changes suggested to occur when Gly-Tyr is bound at the active site. The guanidinium group in Arg-145 moves about 2 Å closer to the carboxylate group of the substrate, while the phenolic group of Tyr-248 moves about 12 Å, with a twisting of the C—C chain so that the OH group lies close to the peptide N. These movements lead to plausible mechanistic features, in which Tyr-248 donates a proton to the NH group of the hydrolyzable peptide link. Furthermore, the closeness of the Glu-270 group to the carboxyl carbon of this group suggests it may have a role in general base catalysis of attack of H_2O or in direct nucleophilic attack on the carbon. Two possible binding schemes are shown in Figure 24. In the zinc carbonyl mechanism, the substrate is bound to zinc by the carbonyl group. The zinc polarizes the carbonyl group and also may serve to orientate the substrate for nucleophilic attack. The role of Glu-270 is not clear. If there is direct nucleophilic attack upon the substrate then an acyl intermediate should be formed. An anhydride intermediate has been found in the hydrolysis of an ester substrate by carboxypeptidase.[508] In the zinc hydroxide mechanism, the susceptible carboxyl bond is directed away from the zinc, while the zinc-bound hydroxide group attacks the substrate.

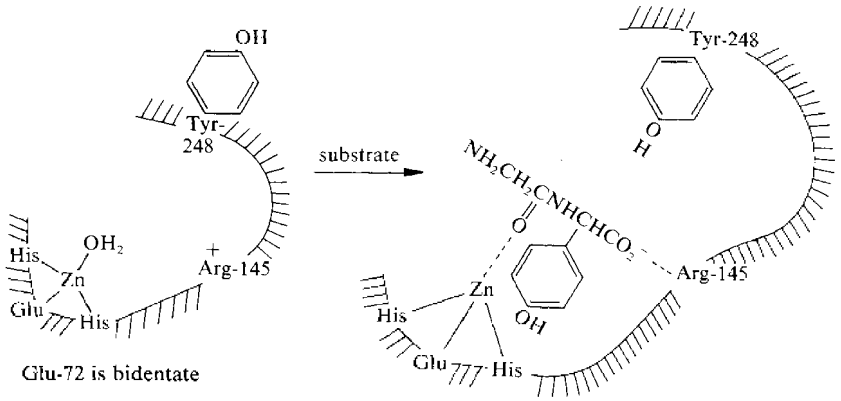


Figure 23 The conformational changes induced in carboxypeptidase on binding of the pseudosubstrate glycyltyrosine

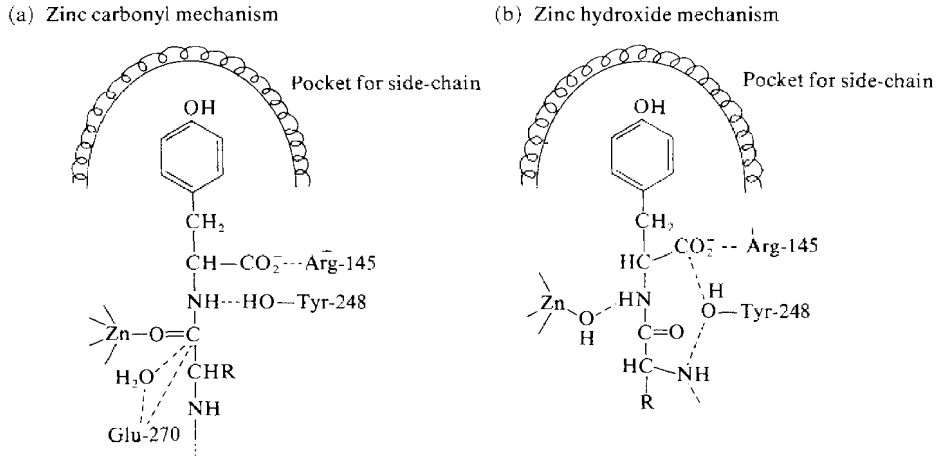


Figure 24 Schemes for the binding of a peptide substrate to carboxypeptidase

Although many of these general features are correct, these mechanistic conclusions are based upon the assumption that the properties of the enzyme in solution are conserved on crystallization. It appears from Raman studies on arsanilazotyrosine-248 carboxypeptidase that the enzyme exists in solution in a number of different forms.[509] It is not certain that the form which crystallizes out is the kinetically active species. Indeed there is evidence that the kinetics of carboxypeptidase in solution differ from those of the enzyme crystals, with the crystalline enzyme being 1000-fold less active with some substrates.[510] The interaction of Gly-L-tyr with Mn^{II} carboxypeptidase A, studied by ^1H NMR techniques, does not involve coordination of the carboxyl group of the substrate, and may well represent a different conformation from the one studied by crystallographic techniques.[511] Several conformational forms of the Cd^{II} carboxypeptidase A have been found in solution, while the enzyme exists in a different form in the crystal state.[512]

62.1.4.3.2 Metallocarboxypeptidases

The zinc in carboxypeptidase may be replaced by a range of metal ions, although most work has been carried out with the Co^{II} enzyme. The structures of the Co^{II} and Ni^{II} enzymes have been determined to 1.7 Å resolution.[513] The detailed geometry of the Co^{II} site is identical to that of the Zn^{II} site within experimental error, while there are some shifts for Ni^{2+} and H_2O in the Ni^{II} enzyme. The Ni^{II} enzyme has previously been assigned an octahedral geometry. If both oxygens of Glu-72 are assumed to act as ligands, then the relative shifts that occur for Ni^{II} and H_2O give an octahedral site in which the sixth position is vacant.

Kinetic studies on metallocarboxypeptidases have given useful insight into the role of the metal ion in peptidase and esterase activities. The data presented in Table 13 show that in peptidase

Table 13 Hydrolysis of Bz-$(Gly)_2$-L-Phe and an Ester Analogue by Metallocarboxypeptidases at 25 °C, pH 7.5

Metal	*Bz-$(Gly)_2$-L-Phe*		*Bz-$(Gly)_2$-L-OPhe*	
	k_{cat} (min^{-1})	$10^3 K_m$ (mol dm^{-3})	$10^{-4} k_{cat}$ (min^{-1})	$10^4 K_m$ (mol dm^{-3})
Co	6000	0.66	3.9	3.03
Zn	1200	1.00	3.0	3.33
Mn	230	0.36	3.6	15.2
Cd	41	0.77	3.4	83.3

activity the K_m value for substrate binding depends only slightly upon the nature of the metal, while the rate constant is metal dependent. The opposite situation holds for esterase activity. This suggests that the primary role for the metal in peptide hydrolysis is associated with catalysis rather than binding, while the converse is true for the hydrolysis of esters.

62.1.4.3.3 Chemical modification of amino acid residues

The role of certain residues in the enzyme mechanism has been confirmed by chemical modification studies, notably for tyrosine.[514] Modification of tyrosyl residues (for example acetylation or nitration) leads to loss of peptidase activity and enhancement of esterase activity. The presence of the inhibitor β-phenylpropionate protects two tyrosine residues from acetylation. Those are Tyr-248 and probably Tyr-198, which is also in the general area of the active site. The modified apoenzyme has lower affinity for dipeptides, as might be expected from the loss of hydrogen bonding between Tyr-248 and the peptide NH group.

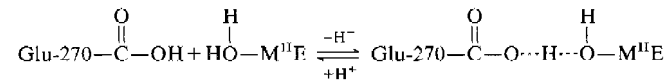
The tyrosine group can be coupled with *p*-azobenzenearsonate to give an asymmetric centre. The CD spectrum changes on addition of glycyl-L-tyrosine, showing that the conformation of the azotyrosyl residue is altered on binding of substrate.

Modifications involving Glu-270 and Arg-145 have not given such positive results. However, modification of arginyl residues in carboxypeptidase by diacetyl results in loss of peptidase activity.

62.1.4.3.4 Kinetic studies and the mechanism of action

The kinetics of action of carboxypeptidase are very complex. The pH–rate profile for CPA-catalyzed hydrolysis of peptides is bell shaped, with apparent pK_a values of about 6.5 and 7.5. The former pK_a value could be attributed to Glu-270. The pH dependency of the kinetics of the CPA-catalyzed enolization of the ketonic substrate[515] (*R*)-2-benzyl-3-(*p*-methoxybenzoyl)propionic acid leads to the establishment (with minimum complications from this relatively simple reaction) of a pK_a value of 6.03 for the Co^{II} and Zn^{II} CPA, which is probably due to Glu-270. The binding of the substrate to both Zn^{II} and Co^{II} CPA appears to depend on an enzyme-bound group with $pK_a = 7.56$ and 8.29 respectively, and on a group with $pK_a > 9$. These are attributed to the ionization of Tyr-248 and the bound water molecule.

The role of Glu-270 has been much discussed. As noted earlier, this could involve general base catalysis of attack of water, or direct nucleophilic attack on the carbon of the hydrolyzable peptide link. Some studies on the interaction of anions with cobalt carboxypeptidase A have thrown light on this question.[516] At pH > 7, the *d–d* and MCD spectra of Co^{II} CPA are insensitive to anions, but at pH < 6, chloride and other anions perturb them in an anion-specific manner. It appears that decrease in pH facilitates entry of the anion into the metal coordination sphere, implying that displacement of the metal-bound water is hindered by some basic group in the enzyme. Modification of Glu-270 in cobalt carboxypeptidase generates sensitivity to anions similar to that of the unmodified enzyme at pH ~ 5. This suggests that the metal-bound aqua group is stabilized by the catalytically essential carboxylate of Glu-270, and so provides evidence for a mechanistically important interaction of Glu-270 with an aqua group (equation 15). This would generate a nucleophilic metal hydroxide that could initiate hydrolysis of the peptide bond. This scheme is consistent with the 4.5 Å distance between the carboxylate of Glu-270 and the metal, and with *ab initio* molecular orbital calculations.[517] Site-directed mutagenesis shows that Tyr-248 does not play a crucial role in catalysis. Proton donation from water or Glu-270 is possible.[518]



(15)

The mechanism of action of carboxypeptidase has also been much studied recently by the techniques of cryoenzymology, which have allowed the identification and characterization of reaction intermediates.[519,520] This has shown the presence of two intermediates during the hydrolysis of both peptides and esters. In conjunction with chemical evidence, this work demonstrates that there is no acyl intermediate in either peptide or ester hydrolysis, and that these two substrates form different metallo intermediates and are hydrolyzed through different mechanisms.

In summary, therefore, it appears that the mechanism of peptide hydrolysis involves the attack of a zinc-bound hydroxide group whose formation is promoted by Glu-270, probably with the formation of a six-coordinate intermediate through binding of substrate.

62.1.4.4 Thermolysin

This zinc endopeptidase has a molecular weight of 34 600 and contains one zinc ion, together with four Ca^{2+} which impart heat stability to the enzyme. The ligands for the four calcium ions are listed in Table 6, while the environment around the Zn^{II} is similar to that found in carboxypeptidase. Zinc is bound by His-142, His-146 and Glu-166 and water, while Glu-143 is able to promote the attack of water on the substrate. There is no residue strictly analogous to Tyr-248 in carboxypeptidase. One difference from carboxypeptidase lies in the fact that Glu-143 is far enough from the carbonyl carbon of the substrate to accommodate an intervening water molecule. It appears that in thermolysin the favoured pathway involves a general base mechanism with six-coordinate zinc having both H_2O and the substrate's carbonyl oxygen coordinated.

62.1.4.5 Aminopeptidases, Particularly Leucine Aminopeptidase

Many aminopeptidases are zinc metalloenzymes.[521] They catalyze the specific hydrolysis of N-terminal amino acids from proteins and peptides, and usually have a broad substrate specificity. The zinc aminopeptidases from mammalian sources are oligomeric, with molecular weights greater than 200 000, and have two moles zinc per mole subunit. Enzymes from microbial sources are usually monomeric (40 000 molecular weight) with one or two moles Zn^{II}.

The best studied aminopeptidase is leucine aminopeptidase from mammalian sources. This has a broader specificity than the name suggests, the sequence for the rate of hydrolysis of N-terminal amino acids being Leu > Phe > Val > Ala > Glu.[522] Bovine lens leucine aminopeptidase is hexameric, with a subunit molecular weight of 54 000. The six subunits are arranged at the vertices of a distorted triangular prism.[523] Chemical modification of residues implicates two histidyl residues per subunit as ligands for zinc, together with cysteine. The zinc can be removed by treatment with 1,10-phenanthroline without effects on the hexameric structure, showing that zinc does not play a structural role. The zinc may be replaced by cobalt, to give an enzyme that is more active than the native zinc enzyme.[524] However, other metal ions cannot replace both zinc ions with retention of activity. Replacement of one zinc by Mg^{II} or Mn^{II} enhances activity.[525] It appears therefore that the binding of one zinc (or cobalt) at one site per subunit is essential for catalytic activity. A range of other metals can bind at the second site on each subunit and regulate the activity induced by the zinc at the first site. Zinc binds much more tightly at the activation site than at the regulatory site.

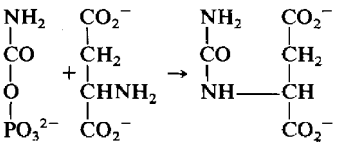
Porcine kidney leucine aminopeptidase also binds one Zn^{2+} per subunit, which is essential for catalysis. The activity of the enzyme is regulated by the binding of divalent metal ions at a second site.

Leucine aminopeptidase catalyzes the transpeptidation reaction Leu-NH_2 → Leu-Leu-NH_2. The product obtained when the reaction is carried out in $H_2{}^{18}O$ contained 50% of the label, suggesting that this reaction also proceeds *via* a general base catalysis mechanism.[526]

62.1.4.6 Aspartate Transcarbamylase

This is an allosteric enzyme that requires zinc for structural stability. It catalyzes the condensation of carbamyl phosphate with L-aspartate to give carbamyl-L-aspartate and phosphate (equation

16). Carbamyl-L-aspartate is the key precursor in the biosynthesis of pyrimidines. The enzyme aspartate transcarbamylase is inhibited by several pyrimidine nucleotides, notably cytidine triphosphate, and is activated by ATP, a purine nucleotide. Thus the enzyme is under feedback regulation, and controls the relative concentration of pyrimidine and purine nucleotides.



(16)

The enzyme from *E. coli* has been much studied. It is oligomeric, of molecular weight 310 000, and dissociates into five subunits on treatment with *p*-mercuribenzoate or other mercurial reagents. Three of these are regulatory subunits R and two are catalytic subunits C, with overall composition C_2R_3. The C subunit is made up of three identical polypeptide chains, each of molecular weight 33 000. The R subunit is made up of two identical polypeptide chains, each of molecular weight 17 000. The enzyme thus consists of 12 polypeptide chains, in groups of trimers and dimers.[527]

The enzyme contains six Zn^{2+} per molecule, two per R subunit. The zinc is not required for catalytic activity, but is essential for the maintenance of the quaternary structure. The structure has been determined to a resolution of 2.8 Å in the presence and absence of CTP.[528] The zinc-binding site is located in the C-terminal region of the R chains, and involves four cysteinyl residues, with tetrahedral geometry. The zinc domain represents the major site of interaction between the R and C chains, explaining the importance of zinc for the association of the subunits and the dissociative effect of mercurial reagents. When *E. coli* is grown in a zinc-deficient medium, some 70% of the enzyme is found to be dissociated into subunits.[529]

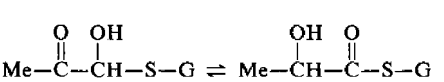
If *E. coli* is grown in a cadmium-containing, zinc-deficient medium, the enzyme is found to be active, but to contain six Cd^{2+} per molecule. The presence of cysteinyl ligands is confirmed by the observation of the characteristic charge-transfer bands. The binding of substrate perturbs the absorption and CD spectra of the zinc and cadmium enzymes, and the *d*–*d* spectrum of the nickel enzyme, showing that the conformation of the R subunit is affected by the binding of substrate to the C subunit.[530,531]

62.1.4.7 α-Amylase

This enzyme, which catalyzes the hydrolysis of glucosides, is a second example where Zn^{2+} may only play a structural role. The enzyme always contains Ca^{2+}, which is necessary for catalytic activity, but the enzyme from *Bacillus subtilis* also contains zinc, which is thought to dimerize two monomeric units. However, there is some doubt over this matter, as the enzyme appears to exist as a monomer–dimer equilibrium in the absence of zinc. Zinc may then bind to the dimer only.[532]

62.1.4.8 Glyoxalase 1

Glyoxalase 1 from yeast and from mammalian sources is a dimeric enzyme, with one Zn^{2+} per subunit, which catalyzes the isomerization of the hemi-mercaptal adduct between glutathione and methylglyoxal to form the thiol ester (equation 17). The reaction involves the conversion of α-keto aldehydes into α-hydroxycarboxylic acids. Studies on the cobalt-substituted enzyme have suggested an octahedral environment around the metal,[533] while water proton relaxation studies with the Mn^{2+}-substituted enzyme have shown two aqua ligands.[534] A second-sphere enzyme–metal–(H_2O)–product complex that is probably involved in catalysis has been detected by studies on the effects of the Mn^{2+}- and Co^{2+}-substituted enzymes on nuclear relaxation rates of the product *S*-D-lactoylglutathione.[535,536] The octahedral geometry around the metal is unusual. Only one other zinc enzyme has been reported to have a six-coordinate zinc, namely transcarboxylase. This was established through ESR studies on the cobalt enzyme.[537]



(17)

X-Ray edge and extended absorption fine structure spectra of zinc at the active site are consistent with a seven-coordinate or distorted octahedral environment.[538] Analysis of the fine structure eliminates sulfur ligands and suggests Zn—N or Zn—O distances of 2.04 and 2.10 Å. These are appropriate for an octahedral complex. There is evidence for atoms at distances of ~3–4 Å from the Zn^{2+}, similar to data on known Zn^{2+}-imidazole complexes and carbonic anhydrases,[539] which may be due to the presence of at least two imidazole ligands. The binding of the heavy atom substrate analogue *S*-(*p*-bromobenzyl)glutathione to glyoxalase 1 does not affect significantly the environment of the zinc, in accord with the NMR evidence for second-sphere product complexes.[535,536] Thus is appears that the ligands for zinc are two imidazoles, two N or O ligands and two or three water molecules.

The mechanism of the glyoxalase 1 reaction is thought to involve polarization of the carbonyl group of the substrate in the forward reaction, and of the product in the reverse reaction.[535] However, the carbonyl oxygen of the product cannot be coordinated to the metal. It is possible that polarization of the carbonyl group occurs indirectly *via* hydrogen bonding to a zinc ligand.

62.1.4.9 Alcohol Dehydrogenase

The alcohol dehydrogenases[466] are NAD(H)-dependent enzymes that catalyze the reversible oxidation of alcohols to aldehydes (equation 18). The enzymes from yeast (YADH) and liver (LADH) have been most studied.

$$RCHO + NAD(H) + H^+ \rightleftharpoons RCH_2OH + NAD^+ \quad (18)$$

LADH is a dimeric enzyme, consisting of two identical subunits of molecular weight 40 000. Each subunit contains two zinc ions and binds one molecule of NAD(H). There appear to be two types of zinc: one is essential for catalysis while the other may have a structural role, although this is not certain. Crystallographic studies on the native enzyme[540,541] and on the Co^{II} and Cd^{II} enzymes[542] show that the catalytic zinc at the active site is bound by His-67, Cys-46 and Cys-174, in a distorted tetrahedral geometry, the fourth ligand being water, which is linked to a hydrogen bonding network involving Ser-48 and His-51. The non-catalytic Zn^{II} ion is coordinated by four cysteine residues (Cys-97, Cys-100, Cys-103 and Cys-111).

Each subunit is made up of two unequal domains. The active site is at the bottom of a hydrophobic pocket, about 25 Å from the protein surface. The non-catalytic zinc, some 25 Å away, is near the surface, but is not exposed to solvent. Both sites are on the larger domain, while the smaller domain provides the site for the coenzyme. Formation of the enzyme–NAD(H) complex induces major conformational changes,[543] in which there is a rotation of the catalytic domain resulting in a narrowing of the active-site cleft.

62.1.4.9.1 Binding of coenzyme

The structure of the coenzyme is shown in Figure 25. Loss of a formal hydride from the 4-position of the nicotinamide ring gives NAD^+. The coenzyme analogue ADP-ribose binds to the enzyme mainly through the interaction of the adenine with a hydrophobic pocket on the enzyme. In addition, there is a salt link between the pyrophosphate group and Arg-47 together with hydrogen bonding between the ribose and Asp-223. The C(4) atom of the nicotinamide is 4.5 Å away from the catalytic zinc. The question of whether or not the metal binds the coenzyme directly is a lively one. The C(4)—Zn^{2+} distance may change in solution to allow this interaction. It has been proposed that the coordination number of the zinc is five in the binary complex with NAD^+.[544] The several possibilities for Zn^{2+}-NAD^+ interaction have been reviewed.[545] However, the wide range of techniques that have been applied have failed to give conclusive evidence for direct metal-coenzyme interaction. Many studies have been inconclusive or contradictory.[466] On the other hand there is some positive evidence for the maintenance of a four-coordinate geometry for the metal in the binary complex. Thus the shape and intensity of the electronic spectrum[546] of $Co(c)_2Zn(n)_2$-LADH (discussed below) are consistent with the expected tetrahedral structure[542] for the catalytic metal ion. However, there are no major changes in the spectrum of the binary complex, suggesting that the four-coordinate structure is maintained and that the coenzyme does not bind to the metal.

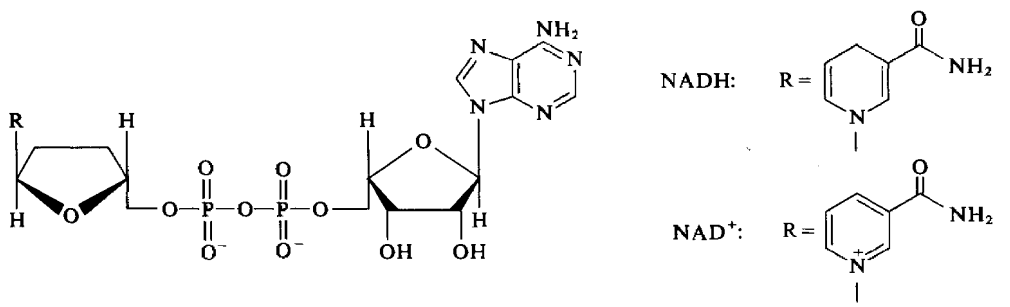


Figure 25 The structures of NADH and NAD^+

62.1.4.9.2 Metal for zinc substitution

The chelating agents 1,10-phenanthroline and 2,2′-bipyridyl and the ligand imidazole inhibit by binding to the catalytic zinc, with displacement of the aqua ligand and the formation of five-coordinate complexes.[547] Dialysis against these chelating agents allows the removal of the zinc for LADH but not YADH. The catalytic atoms are active to 1,10-phenanthroline but the non-catalytic pair are not.[548] In contrast, the non-catalytic atoms exchange more rapidly than the catalytic zinc ions, possibly due to the position of the latter ions at the bottom of the cleft.

It is now possible to define conditions under which the catalytic or the structural zinc can be specifically replaced.[548,549] This allows the preparation of hybrid Co^{II}, Zn^{II} enzymes, in which the Co^{II} is at the catalytic (c) or non-catalytic (n) sites.[550]

62.1.4.9.3 Binding of substrate

The suggestion that the zinc in alcohol dehydrogenase bound and polarized the carbonyl group of substrate aldehyde is of long standing.[551] The suggestion of substrate oxygen–zinc interaction is supported by X-ray diffraction studies,[540,541] and by kinetic studies on the reduction of *trans*-4-(*N,N′*-dimethylamino)cinnamaldehyde by LADH and NADH.[552] Binding of the aldehyde by Zn^{2+} leads to activation for hydride attack, followed by hydride transfer from NAD(H), proton transfer to the resulting Zn-bound alcoholate ion, and product release.[553] A comparison of the rates of reduction of benzaldehydes by LADH/NAD(H) and borohydride is illuminating. The ratio of rate constants for the reduction of *p*-chloro- and *p*-methoxy-benzaldehyde by borohydride was 100 to 1, while for enzymatic reduction the ratio was 2 to 1. The lack of any effect from the substituent on the enzymatic reaction was attributed to the effect of polarization of the carbonyl bond by coordination to zinc.[554] Direct coordination of substrate to the zinc is supported by other kinetic studies,[555] and by elegant studies in solution using NMR techniques and spin-labelled ligands.[545,555] Similar conclusions have been reached for YADH,[557] and for the cobalt-substituted LADH.[558,559]

Substrate–apoenzyme interaction occurs, however, and this has led to the suggestion[560] that there is no metal ion–substrate interaction. It may be, of course, that the substrate binds to a completely different site on the apoenzyme, or that weaker interaction occurs, reflecting the absence of the metal.

The *Z* isomer of the model substrate 4-*trans*-(*N,N′*-dimethylamino)cinnamaldoxime (*Z*-DMOX) forms a ternary complex with NAD^+ and LADH. The Co^{II}, Ni^{II}, Cu^{II} and Cd^{II} enzymes (with the metal substituted for the catalytic zinc) and the apoenzyme also form ternary complexes with *Z*-DMOX.[561] The affinity of the apoenzyme–NAD^+ complex for *Z*-DMOX is much lower and the rate of *Z*-DMOX dissociation from the apoenzyme complex was 10^3-fold greater than the rates found for the metal-substituted enzymes. Complex formation results in a red shift (43 to 83.5 nm) in the DMOX UV-visible spectrum, due, it is suggested, to bonding of the oxime nitrogen to a strong electrophilic centre, either the Zn^{2+} or the nicotinamide ring of NAD^+, a view that is compatible with the known structural features of the LADH/NADH/Me_2SO complex. The high affinities and slow rates of dissociation of the metal-substituted enzyme complexes are attributed to the coordination of *Z*-DMOX to the active site metal.[561]

62.1.4.9.4 Kinetic studies and mechanism of action

At least four protonation-deprotonation equilibria have been implicated in catalysis, having pK_a values 6.4, 7.6, 9.2 and 11.2.[562,563] The pK_a of 9.2 has been attributed to the deprotonation of the zinc-bound water, and the values of 7.6 and 11.2 to its deprotonation in the binary complexes with NAD^+ and NAD(H) respectively.[563–565] The pK_a value of 6.4 has been assigned to the deprotonation of the zinc-coordinated alcohol.[566] The electronic spectra of $Co(c)_2Zn(n)_2$-LADH and its binary complex with NAD^+ are pH dependent, with pK_a values of around 8 and 9 respectively.[567] These have been related to the pK_a values of 7.6 and 9.2 reported for the Zn_4 enzyme described above. The electronic spectrum of the binary complex of $Co(c)_2Zn(n)_2$-LADH with NADH is independent of pH in the range 6 to 9.

The origin of these pK_a values has been explored by ^1H NMR studies on cobalt LADH,[546] which suggest that the pK_a value of 9.0 in $Co(c)_2Zn(n)_2$-LADH is due to the δ-NH group of His-67, one of the ligands. In the complex with NAD^+ the same group shows a pH-dependent shift without deprotonation, with a pK_a of 8.3 ± 0.2, which is suggested to correspond to the pK_a of 7.6 obtained from kinetic data on the native enzyme, and to be due to coordinated water. The suggestion that His-67 is involved in the acid–base equilibria is novel and requires substantiation.

Evidence has been given in Section 62.1.4.9.3 for the coordination of substrate to the active site zinc. The zinc appears to become five-coordinated when ROH is bound.[569] The active species may involve the hydroxide group, which is stabilized by hydrogen bonding to Ser-48, which is hydrogen bonded to His-51. Hydride-transfer to NAD^+ from the CH_2 group of ROH then occurs, with loss of the proton to the bound hydroxide. However, many aspects of the mechanism await clarification. The role of the zinc appears to be that of polarization of the susceptible C—O bond and to lower the pK_a of a water molecule at the active site. There is no experimental evidence to support an assignment of any role to the non-catalytic zinc. *E. coli* alkaline phosphatase also contains zinc ions of unknown function. The mechanism is represented in Figure 26.

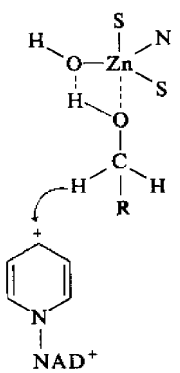


Figure 26 Mechanism of action of alcohol dehydrogenase

62.1.4.10 Alkaline Phosphatase

This enzyme is a non-specific phosphomonoesterase that shows maximum activity at pH values greater than 8.[569] It also catalyzes the transfer of phosphoryl groups. These reactions involve the formation of a phosphoseryl intermediate and the hydrolyzed substrate. The phosphoenzyme may transfer the phosphoryl group to water or to an acceptor molecule to give a new phosphoester (equations 19 and 20, where E—P represents the covalently bound phosphoenzyme and E·P a non-covalent complex, in which phosphate is coordinated to the zinc). The phosphoenzyme may be formed from either direction.

$$E + ROP \rightleftharpoons E \cdot ROP \rightleftharpoons E{-}P + RO^- \quad (19)$$

$$E{-}P \rightleftharpoons E \cdot P \rightleftharpoons E + P_i \quad (20)$$

Alkaline phosphatase is well known to be involved in mineralization, possibly through hydrolysis of organic phosphates to raise the product $[Ca^{2+}][P_i]$ to a level where precipitation occurs.

62.1.4.10.1 Structural aspects

The enzyme from *E. coli* has been most studied. As isolated, it contains up to four Zn^{2+} and two Mg^{2+} per molecule. It is cleaved into two subunits on treatment with acid. The amino acid sequence[570] and structure are known.[571] The sequence gives a molecular weight of about 94 000. It contains very high levels of four residues (Gly, Ala, Glu, Asp), which account for about 40% of the amino acid residues of the enzyme.

It is now established[572,573] that each monomer in the apoalkaline phosphatase dimer contains three metal ion-binding sites, designated A, B and C, lying within 4 to 7 Å of each other in a triangular cluster. This is represented schematically in Figure 27. The metal at site A is bound by three histidyl residues, and is about 4 Å from site B. Site B has one histidyl ligand together with carboxyl ligands. It binds Mg^{II} as well as Zn^{II} or Cd^{II}. Site C is about 7 Å from A and involves oxygen ligands. It binds Mg^{II} and Cd^{II}. For maximum activity, sites A and B must be fully occupied by Zn^{II} (four in total), or site A may have Zn^{II} and site B Mg^{II}. Occupancy of site C does not affect reactivity. The use of NMR techniques for the ^{113}Cd enzyme with either ^{31}P or ^{13}C substitutions has contributed greatly to the elucidation of these sites.[282]

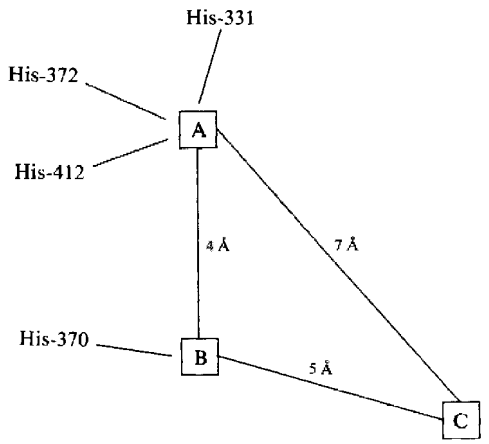


Figure 27 Metal-binding sites in alkaline phosphatase

62.1.4.10.2 Metal substitution in alkaline phosphatase

Much attention has been paid to metal-substituted alkaline phosphatases, notably Co^{II} (*d–d* spectra), Mn^{II} (ESR) and Cd^{II} (^{113}Cd NMR). The apoenzyme may be prepared by use of ammonium sulfate to remove zinc.[574] After about five days the apoenzyme may be isolated having less than 3% of the original zinc. Furthermore, the apoenzyme is uncontaminated by chelating agents, which show a tendency to bind to the apoenzyme. A range of metalloalkaline phosphatases may be prepared from the apoenzyme. The binding of cadmium^{II} at three separate sites can be confirmed by the use of ^{113}Cd NMR, which shows[574] three separate resonances at 153, 72 and 3 p.p.m. in the phosphorylated dimer $^{113}Cd^{II}{}_6AP$. When all three sites are occupied by Cd^{II}, the enzyme has a very low turnover, at least 10^3 times slower than the native Zn^{II} enzyme. This slow turnover number has made the Cd^{II} enzyme particularly useful in NMR studies.

Mg^{II} competes only for the B sites. Binding of metal ions to the apoenzyme appears to be a cooperative process involving conformation changes. Metal ions bound at the C sites dialyze readily without detectable change on the structure and function of the enzyme.

Detailed studies on the thermodynamics of binding of Zn^{II}, Cd^{II}, Co^{II} and Mg^{II} are available.[575] The sites A, B and C bind metal ions with decreasing affinity. In the case of Cd^{II}, binding of the first two Cd^{II} occurs at 5×10^{-5} mol dm^{-3} [Cd^{II}]. However, this is part of a smooth binding curve which results in binding of six Cd^{II} per dimer at 10^{-3} mol dm^{-3} [Cd^{II}]. Nevertheless, the enzyme at pH 6.5 with only two Cd^{II} bound per dimer shows a single ^{113}Cd NMR resonance. This confirms that binding of the first two Cd^{II} takes place at the binding sites A on each monomer, and that this is complete before binding at B takes place. However, binding at these and other sites is dependent upon pH, phosphate and magnesium concentrations, and upon occupancy of other

sites, showing the binding to be cooperative. Thus addition of phosphate enhances the affinity of site B for Cd^{II}, so that a second pair of Cd^{II} can be induced to bind at lower [Cd^{II}]. Alternatively, covalent phosphorylation at one active site in Cd^{II}_2AP results in the appearance of two resonances in the ^{113}Cd NMR spectrum, due to the formation of a species with $^{113}Cd^{II}$ bound to an A site and a B site on the phosphorylated monomer, and with the sites on the non-phosphorylated monomer unoccupied. Increase in pH stabilizes the B site. Thus, for the non-phosphorylated enzyme Cd^{II}_2AP, the single resonance observed at pH 6.5 is replaced[576] by two resonances in the ^{113}Cd NMR spectrum at pH 7.5. The increase in pH has increased the affinity of the B site so that occupancy of A and B sites on one monomer and none on the other is more favoured. It has been pointed out[282] that an ESR investigation of the Mn^{II}_2AP should give evidence for the migration of the metal ion upon raising the pH or upon monophosphorylation, since two Mn^{II} centres separated by only about 5.8 Å should show spin–spin exchange detectable in Mn^{II} ESR spectra.

Arsenate competes with phosphate for its binding site. The enzyme Cd^{II}_2AP binds arsenate at one monomer. This causes the migration of Cd^{II} from the A site of one monomer to the B site of the arsenylated monomer, as found for phosphate.[577]

Methods have been developed[578] for the selective addition of metals to the various pairs of sites, so allowing the preparation of hybrid alkaline phosphatases, for example $(Zn^{II}_A Cd^{II}_B)_2$ alkaline phosphatase, $(Cd^{II}_A Zn^{II}_B)_2$ alkaline phosphatase and $(Zn^{II}_A Zn^{II}_B)(Cd^{II}_A Cd^{II}_B)$ alkaline phosphatase. The availability of these hybrids has led to a clearer picture of the functions of the different sites.

62.1.4.10.3 Mechanism of action

The roles of the different metal sites have been clarified. The A site metal (Zn^{II} in the native enzyme) serves to coordinate phosphate to give the non-covalent complex. The phosphate is then transferred to Ser-102, with its coordination site on the A site metal being filled by solvent. Phosphorylation of the Ser-102 is accelerated by the B site metal ion, probably due to additional charge neutralization of the negative phosphate as it moves towards Ser-102. There appears to be no evidence for direct coordination of the phosphate to the B site metal ion. Dephosphorylation of the phosphoserine is accelerated at alkaline pH, possibly due to a large increase in concentration of a zinc-bound hydroxide group formed by ionization of the A site aqua group. Nucleophilic attack of hydroxide is followed by rate-determining dissociation of product phosphate.

The cooperative interactions in alkaline phosphatase have not been fully clarified. Examples have been given to show that the binding of metal or phosphate at one monomer affects the other monomer. Such phenomena must involve the transmission of conformational information through the interconnecting polypeptide structures. Trypsin modification of *E. coli* alkaline phosphatase results in the loss of a decapeptide from the amino terminus of each monomer which occurs at the subunit interface region in the native structure.[579] This results in a decrease of activity which has been assigned to an increased affinity for P_i, which thus lowers the rate-limiting dissociation of P_i. The use of differential scanning calorimetry confirms that loss of the decapeptide appears to alter substantially the overall structure of the protein. Thus it is feasible that the reactivity of alkaline phosphatase is controlled by the transmission of allosteric effects between subunits.

The M^{II}_2AP form (M = Zn, Cd) binds only one mole of phosphate per mole of enzyme, thus showing negative cooperativity. When sites A and B are occupied, two phosphate ions bind. Thus the occupancy of site B induces the binding of phosphate at the second phosphate site.[580] This type of behaviour may underlie the function of the metal ion in the modulation of enzymatic activity. Phosphorus-31 NMR shows that Mn^{II}_2AP binds one mole of phosphate. This induces dramatic changes in the ESR spectrum of the enzyme, suggesting that the binding of phosphate alters the conformation at site A. The application of differential scanning calorimetry techniques suggests that the $2Cd^{II}$ phosphoryl enzyme has a second binding site for phosphate.[581]

62.1.4.11 The β-Lactamases

Both zinc metalloenzyme and non-metalloenzyme forms of this enzyme are known. These catalyze the hydrolysis of the β-lactam ring of penicillins and the related cephalosporins, so inactivating them as antibiotics. The β-lactamases are therefore of considerable medical importance as they are involved in the development of resistance to penicillin in pathogenic bacteria.

Bacillus cereus produces β-lactamase I and β-lactamase II. The former does not contain zinc.[582] The β-lactamase II binds two Zn^{II} per molecule. The use of 270 MHz ^1H NMR spectroscopy shows that resonances attributable to three of the histidyl residues in the apoenzyme shift on binding one Zn^{II} per molecule, while resonances due to the fourth histidyl residue shift on binding of a second Zn^{II}.[583] There is one cysteinyl residue, which has also been suggested to act as a ligand, on the basis of spectroscopic studies of the Co^{II} enzyme.[584]

62.1.4.12 Phospholipase C

Phospholipase C from *B. cereus* contains two zinc ions per molecule of protein (molecular weight 23 000), the two metal ions being about 5 Å apart. The zinc appears to have a particular role in the stabilization of the protein structure.[585] Added Zn^{II} protects the enzyme against denaturation and induces the refolding of the denatured enzyme. Other metals are much less effective than zinc in carrying out this function.[586]

62.1.4.13 Fructose-1,6-bisphosphatase

The enzyme from various sources is tetrameric. There is some confusion about the number of sites for zinc on each subunit, but probably there are three, giving a total of 12 Zn^{2+} bound per molecule.[587,588] The role of Zn^{2+} appears to be one of modulation of activity. Binding of Zn^{II} to the first two sets of binding sites results in reduced catalytic activity. The third set of sites (of lowest affinity) appears to be the sites for the activating cation Mg^{2+}. Thus Zn^{II} can act as a negative regulator of fructose-1,6-bisphosphatase, and also as an activator when it binds to the third set of sites.

62.1.4.14 Zinc and Snake Venoms

Snake venom is a complex misture of proteins with various biological activities.[589] These include neurotoxins, cardiotoxins, cytotoxins, hemorrhagic toxins and myotoxins, together with anti- and pro-coagulants of blood, and enzymes such as phospholipase A_2, phosphodiesterases, phosphatases, proteolytic and other enzymes. The venoms contain large amounts of metals, particularly Na^+. The Na^+ is probably present as a neutralizer of charge, and is largely lost on prolonged dialysis. Zinc is present in the concentration range 300–1400 $\mu g\ g^{-1}$ venom.

Nerve growth factor is commonly found in snake venoms. This is a protease with specificity for lysyl and arginyl bonds, which contains one Zn^{2+} per molecule. The function of the zinc is to prevent the activation of NGF, presumably through control of the structure. Removal of Zn^{II} from NGF with EDTA leads to activation of the zymogen.

Zinc is also found in purified hemorrhagic toxins and proteolytic enzymes from venoms. Fibrinogenase is a proteolytic enzyme which renders fibrinogen unclottable. This has one Zn^{2+} per molecule of protein.[590] Further examples include a peptidase from the venom of *Agkistrodon piscivorus leucostoma*,[591] a proteinase from *Trimeresurus flavoviridis*,[592] and proteolytic enzymes from *Crotalus atrox*[593] and *Agkistrodon acutus*.[594]

62.1.4.15 Some General Conclusions

The examples given in the preceding pages have demonstrated that zinc in metalloenzymes may have catalytic, regulatory or structural functions. In addition there are some cases where the zinc appears to have no obvious function. Its most common role is that of catalysis, while a structural role has been demonstrated conclusively in only two cases, aspartate transcarbamylase and *B. subtilis* α-amylase.

In a number of cases, a common pattern for catalytic activity seems to be developing, where the zinc centre, already four-coordinate with three protein ligands and an aqua group, binds the substrate to give a five-coordinate complex. The zinc-bound aqua group is ionized to give hydroxide, which participates in the catalytic reaction. Changes in coordination number of the zinc from four to five and back to four appear to be a common feature of zinc metalloenzymes.

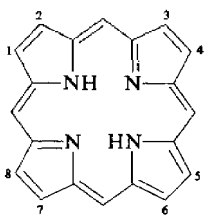
62.1.5 THE BIOCHEMISTRY OF IRON — A SURVEY OF IRON-CONTAINING ACTIVE SITES

The importance of iron in biology needs no emphasis. It is present in a range of hemoproteins, including the oxygen carriers hemoglobin and myoglobin, the cytochrome electron-transfer catalysts, and enzymes such as cytochrome P-450, cytochrome oxidase, peroxidase and catalase. Non-heme iron proteins include the iron–sulfur proteins and a range of dinuclear oxo-bridged proteins such as hemerythrin. In this section it is planned to emphasize fundamental aspects of the structure and reactivity of these iron proteins, and to study further their biological function in subsequent sections.

62.1.5.1 The Iron Porphyrins

The chemistry and biochemistry of the porphyrins have been comprehensively reviewed,[595,596] both as the prosthetic group of hemoproteins and in their own right. The basic structure of the porphyrin group has been discussed briefly in Section 62.1.1. This is shown again in Table 14, which also gives the substituents present in some naturally occurring porphyrins, for which all eight pyrrole carbon atoms are fully substituted. The nature of these side-chains is important, as they provide stabilizing interactions between the heme group and the proteins in hemoproteins.

Table 14 Some Naturally Occurring Porphyrins



Porphyrin	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Protoporphyrin	Me	$CH{=}CH_2$	Me	$CH{=}CH_2$	Me	$CH_2CH_2CO_2H$	$CH_2CH_2CO_2H$	Me
Hematoporphyrin	Me	CHOHMe	Me	CHOHMe	Me	$CH_2CH_2CO_2H$	$CH_2CH_2CO_2H$	Me
Etioporphyrin	Me	Et	Me	Et	Me	Et	Me	Et
Deuteroporphyrin	Me	H	Me	H	Me	$CH_2CH_2CO_2H$	$CH_2CH_2CO_2H$	Me
Mesoporphyrin	Me	Et	Me	Et	Me	$CH_2CH_2CO_2H$	$CH_2CH_2CO_2H$	Me
Chlorocruoroporphyrin	Me	CHO	Me	$CH{=}CH_2$	Me	$CH_2CH_2CO_2H$	$CH_2CH_2CO_2H$	Me
Coproporphyrin	Me	$CH_2CH_2CO_2H$	Me	CH_2CH_2OH	Me	$CH_2CH_2CO_2H$	$CH_2CH_2CO_2H$	Me
Rhodoporphyrin	Me	Et	Me	Et	Me	CO_2H	$CH_2CH_2CO_2H$	Me

One notable feature of the hemoproteins is the way in which closely similar iron porphyrin groups, when combined with different proteins, can catalyze a diverse range of redox reactions. It thus appears that the particular function of an iron porphyrin is controlled by subtle effects of the protein on the heme group. The protein provides the axial ligands to the iron in the heme and also controls the nature of the local environment of the heme. Thus, in the oxygen carrier hemoglobin the protein provides one axial ligand and protects the 'vacant' second axial position making it available for binding of molecular oxygen.

The structure of the important protoporphyrin IX of heme *b* is shown in Figure 28. This structure lacks any covalent link to the protein, which is attached to the porphyrin only through the provision of the axial ligands. Heme *c* is derived from the heme *b* structure by adding protein cysteine thiol residues across the two vinyl groups. Heme *a* is also related to heme *b*: one vinyl group is changed into a polyene side-chain, while one of the methyl groups is converted into a formyl group. A prosthetic group recognized to be of increasing importance is siroheme, which is a tetrahydroporphyrin derivative. Also shown in Figure 28 is the Fe^{II} complex of tetraphenylporphyrin, which is much used as a model compound. A wide range of other porphyrins have been synthesized with different substituents in the periphery, or as covalently linked dimers, in order to mimic various biological functions such as reversible oxygenation, electron transfer and energy transfer. Many of these will be discussed later.

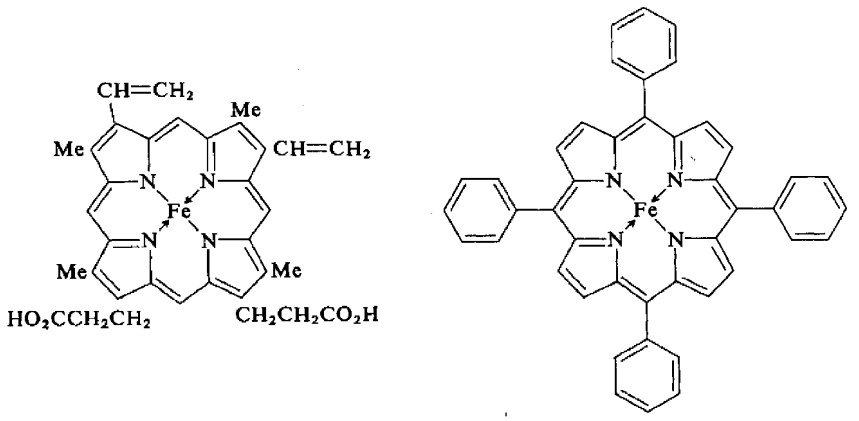


Figure 28 Structures of Fe^{II} protoporphyrin and Fe^{II} tetraphenylporphyrin

62.1.5.1.1 The coordination chemistry of porphyrins

Simple metalloporphyrins are necessarily four-coordinate but they may bind additional ligands in the axial positions. Five-coordinate complexes are square pyramidal, with the metal displaced out of the plane of the porphyrin towards the axial ligand. Binding of a second axial ligand gives a six-coordinate, octahedral complex. Many studies on aspects of the coordination chemistry of porphyrins have laid a solid foundation for the detailed understanding of their geometry,[597] magnetochemistry and stereochemistry,[598] and for the assessment of the significance of the '*trans*' and '*cis*' effects.[599] The complexing ability of porphyrins and related macrocycles is manifested in the formation of complexes with most metals[599] and metalloids[600] in the Periodic Table. These complexes have various applications, for example as photosensitizers in the reduction of water.[601,602]

Transition metal porphyrins with diatomic ligands have received particular attention in view of their special relevance to biological systems. These diatomic ligands include O_2 (obviously, see Section 62.1.12), CO,[603,604] CS[605] and NO.[606,607] The IR and resonance Raman spectra of porphyrins with these axial ligands have been well studied, for example Co^{II} tetraphenylporphyrin.[608]

Porphyrins with metals other than iron (and cobalt) are not of particular direct relevance to the present section, although it should be noted that porphyrins have been extracted from coal and oil shales with metals such as gallium and the early transition metals coordinated. The biological significance of these observations is questionable. Nevertheless, detailed studies on a range of metalloporphyrins have contributed substantially to our appreciation of the bonding in such molecules, and the influence of *cis* and *trans* ligands on their structure and reactivity.[599,609]

The investigation of porphyrins with Ru^{II} and Os^{II} is probably of greater interest[610] for comparison with Fe^{II} porphyrins. These show enhanced metal (d_π)-porphyrin(π^*) backbonding that is manifested in additional features of their electronic spectra. Similarly the resonance Raman spectra of bis(pyridine) adducts of Fe^{II}, Ru^{II} and Os^{II} octaethylporphyrin are sensitive to the nature of the metal, and probably reflect changes in metal–porphyrin σ- and π-bonding, porphyrin core size and charge on the metal.[611] A substantial correlation is available for the effect of axial ligation on the electronic spectra of metalloporphyrins.[612]

A number of unusual structural features have been noted. The ruthenium porphyrin formed by reaction of triruthenium dodecacarbonyl with an *N,N'*-vinyl-bridged tetraphenylporphyrin involves disruption of a pyrrole C–N bond to give a product in which the ruthenium is bound to two pyrrole N atoms, the C and N atoms of the ruptured pyrrole ring, and two mutually *cis* carbonyl ligands. The remaining pyrrole N is uncoordinated.[613] Mutually *cis* configurations have also been found for the dicarbonyl complex of molybdenum tetraphenylporphyrin and for some dinitrosyl porphyrins.

Porphyrins in which the metal is bound to fewer than four pyrrole nitrogen atoms have attracted attention as models for the early steps in the metallation of the macrocycle. The bis[chloromercury(II)] complex of *N*-tosylaminooctaethylporphyrin involves one mercury coordinated to three porphyrin N atoms and one Cl, and the other to Cl and the remaining pyrrole N atom.[614]

A wide range of dimeric porphyrins have been synthesized with specific objectives. Recent examples include face-to-face dimers in which the porphyrins are linked by bridges located at

either the transverse *meso* or β positions of the ring. The gap between the porphyrins can be controlled by the length of the bridge. Such linked dimers have been used for the interactive binding and reduction of dioxygen.[615,616] Modified porphyrins used as models for dioxygen transport are discussed in Section 62.1.12.

Other dimeric porphyrins involve bridging ligands between the metal centres. Thus two Fe^{II} centres have been bridged by imidazolate in order to monitor antiferromagnetic interactions,[617] while nitride[618] and oxide have also been used as bridging ligands. The dinuclear porphyrins $[O_3M_2(TPP)_2]$, where $M = Nb^V$ or Mo^V, involve a triple oxide bridge in the case of the niobium compound (with coordination number seven), while the molybdenum compound has a single Mo—O—Mo bridge with two terminal Mo=O groups.[619]

Porphyrins have been synthesized with the crown ether benzo-15-crown-5 attached at the methine position.[620] Binding of K^+, Ba^{2+} or NH_4^+, which form 1:2 complexes with crown-5 ligands, promotes dimerization of the porphyrins (with a separation of the porphyrin planes of ~4.2 Å).

62.1.5.1.2 Solution studies: complex formation

Studies on porphyrins in aqueous solution are complicated by their lack of solubility (in acidic solutions) and their tendency to associate (in basic solutions). These difficulties may be overcome by using soluble porphyrins with carboxylate or sulfonate substituents, although the uroporphyrins are convenient to study as they are freely soluble, and do not aggregate at concentrations necessary for many solution studies.

The mechanism of incorporation of metal ions into porphyrins has been intensively studied, and has been reviewed frequently.[621-624] These reactions are usually slow, the rate-determining step having been variously attributed to (a) deformation of the porphyrin so that the lone pairs of the nitrogen atoms can be directed away from the porphyrin cavity, (b) proton dissociation from a metal species to give an active form, or (c) complex formation. Mechanisms that involve the deprotonation of the pyrrole nitrogen atoms preceding the rate-determining step have been ruled out for the reaction between Zn^{II} and hematoporphyrin IX in basic aqueous solution.[625] The rapid incorporation of Cu^{II} into porphyrins in the presence of bromide ions has been attributed to the formation of a Cu^{II} complex with Br^- in which the remaining inner-shell aqua groups are labilized.[626] In general, the presence of electron-withdrawing substituents on the porphyrin decreases the basicity of the porphyrin donor atoms, and is reflected in decreased rates of metal binding. The reverse reaction of demetallation in acid solutions has also been studied.[627]

The insertion of ferrous iron into the porphyrin ring in the biosynthesis of heme is catalyzed by the enzyme ferrochelatase. A deficiency in ferrochelatase activity results in an accumulation or the excretion of unchelated protoporphyrin in patients with erythrohepatic protoporphyria. Ferrochelatase catalyzes the synthesis of a range of metalloporphyrins,[628] and, for example, produces zinc protoporphyrin in erythrocytes of patients with iron-deficiency anaemia.

Formation constants for the binding of axial ligands have been reported for many systems, for example pyridine with Fe^{II} and Fe^{III} tetraphenylporphyrin,[629] other Fe porphyrins[630,631] and Co^{II} protoporphyrin IX dimethyl ester.[632] Kinetic studies on the binding of axial ligands are also available.[633,634]

The dimerization of dicyanohemin, monitored by ^1H NMR relaxation studies, has been attributed largely to hydrophobic interactions.[635] NMR techniques have also been used to study dimer formation for Zn^{II} *meso*-nitrooctaethylporphyrin and Zn^{II} α,β-*meso*-dinitrooctaethylporphyrin. In both structures there is interaction between the Zn^{II} of one molecule and the most electron-rich pyrrole subunit of the adjacent molecule.[636]

62.1.5.1.3 The redox chemistry of iron porphyrins

The control of redox potential in a general and a precise manner underlies the function of the porphyrin group in the cytochromes and other hemoproteins. Thus, the redox potentials of cytochromes vary from +380 mV to −500 mV.[637] The factors that control these potentials have been reviewed.[638] Fine control probably reflects the presence of the protein through the effects of charge and hydrogen bonding, but the nature of the substituents on the porphyrin ring and the axial groups on the iron exercise a broad control, although the axial ligands are more important.

Substituents on the porphyrin affect the redox potential, in that reduced basicity of the pyrrole N donor atoms results in a destabilization of the Fe^{III} state.

The influence of the axial ligand follows its donor strength. Strong σ-donors stabilize the Fe^{III} state, but π-acceptor properties exert the opposite effect. The importance of these factors is influenced by the spin state of the iron. Increase in donor strength of the axial ligand causes stabilization of Fe^{III}, but eventually results in the formation of a low-spin complex. This occurs first for the Fe^{II} complex, and so results in stabilization of the Fe^{II}, particularly for π-acceptor ligands. However, once the donor strength of the axial ligand is sufficient to make both Fe^{II} and Fe^{III} low-spin, then further increase in donor strength enhances the stability of the Fe^{III} porphyrin once more.

A particularly interesting comparison is that between a cytochrome with methionine and histidine as axial ligands (as in cytochrome *c*) and one with two histidine axial ligands (as in cytochrome b_5), which have redox potentials of +260 mV and +20 mV respectively. Nitrogen is a better donor than sulfur, and sulfur is the better π-acceptor ligand, so the replacement of histidine by methionine results in the stabilization of the Fe^{II} state in cytochromes. Measurements of redox potentials of iron porphyrin model compounds with imidazole/imidazole and imidazole/thioether axial ligands give a difference of 146–168 mV.[639] This suggests that the protein is responsible for the remaining difference in potential. A number of model studies on thioether/imidazole-ligated iron porphyrins are available.[640]

It will be worthwhile at this stage to bring forward some results on cytochromes that indicate how the effect of the axial ligands on redox potentials may be assessed. This method[641] involves the study of the near IR optical absorption spectra of Fe^{III} low-spin cytochromes. These absorptions are due to charge-transfer transitions from the filled porphyrin $a_{2u}(\pi)$ and $a_{1u}(\pi)$ orbitals to the half-full d_{yz} orbital of the Fe^{III}. The addition of the electron to the Fe^{III} is assumed to involve two hypothetical steps: (i) the excitation of an electron from the $a_{2u}(\pi)$ orbital into the iron d_{yz} orbital, and (ii) the addition of an electron to the $a_{2u}(\pi)$ orbital to give the ground state $iron^{II}$ protein. The energy of the first step is given by the charge-transfer frequency, which depends almost entirely on the axial ligands. The energy of the second step corresponds to the electron affinity of the excited Fe^{III} state, and in turn to the electrostatic environment of the protein. The energy of the $a_{2u}(\pi)$ orbital is relatively insensitive to changes in both axial ligand and the protein. This model suggests that the major effect of change of axial ligand on the redox potential is given by the change in frequency of the charge-transfer band. The replacement of methionine by imidazole in cytochrome *c* results in an increase in charge-transfer frequency of 800 cm^{-1}. This corresponds to a decrease in redox potential of 100 mV, which should be compared to the value given for model porphyrins of 146–160 mV.

It should be noted that the iron centre in porphyrins can be oxidized to high oxidation states, notably in the reactions of peroxidase and catalase. These oxidizing equivalents may rest on the porphyrin ring, generating π-radical cations. Such radical cations can be generated chemically, electrochemically and photochemically. Thus a triplet ESR spectrum has been observed for a copper porphyrin radical cation produced by γ-radiolysis in tetrachloroethane at 77 K. In this case, one electron was localized in the $3d_{x^2-y^2}$ orbital of the copper, and the other was delocalized in the highest occupied π-orbital of the porphyrin ring.[642]

62.1.5.1.4 Electronic effects in iron porphyrins

The biological function of the heme group in hemoproteins will be affected by the axial ligand and the nature of the porphyrin. In the binding of O_2 (and other small molecules), the axial ligand has a *trans* effect which is manifested in kinetic and thermodynamic effects. Again, the selection of axial ligands is central to the control of redox potentials of cytochromes. Axial ligands also exert *cis* effects on the porphyrin, and hence on the metal. The electronic spectrum of the porphyrin is sensitive to the axial ligand, showing the presence of the *cis* effect.

The electronic spectra of porphyrins contain three absorptions, the α, β and Soret bands, with the α band at longest wavelength and the Soret band of greatest intensity. In zinc tetraphenylporphyrin, for example, the three bands occur at 589, 548 and 419 nm, and are π–π^* transitions of the porphyrin ring. These are sensitive to the substituents on the ring and to the axial ligand. The spectrum is metal sensitive also, being shifted to higher energy for metalloporphyrins with d^5–d^9 ions, in accord with the d_π donor ability of the metal. In other instances, additional absorptions are seen, possibly due to porphyrin-to-metal charge transfer. These bands appear to be more sensitive to the nature of the axial ligand. They have been observed for Fe^{III} porphyrins. The

various types of *cis* and *trans* effects in metalloporphyrins have been discussed in detail for axial ligands of σ-donor, σ- and π-donor, and σ-donor/π-acceptor properties.[599]

Several research groups have prepared extensive ranges of Fe^{III} porphyrins with various axial ligands. These have included examples where the axial ligands are (a) thiolate on the one hand, and a nitrogen base, a thiol or thiol ether, or an oxygen donor on the other;[643] (b) imidazole and imidazolate;[644] (c) weak nitrogen donors;[645] and (d) thiolates.[646] In the last case single crystal ESR g determinations were used to give a description of the spin distribution and the axial ligand binding. Analysis of the crystal field parameters obtained from the principal g values show a correlation between the extent of tetragonality and the pK_a value of the thiol. The rhombicity of these complexes was virtually independent of the σ-donor strength of the ligand.

The magnetic properties of the iron porphyrins may be considered in terms of their tetragonal symmetry, which results in the existence of three possible spin states. For the d^5 Fe^{III} centre these are the low-spin $S=\frac{1}{2}$ state, the intermediate-spin $S=\frac{3}{2}$ state and the high-spin $S=\frac{5}{2}$ state. Examples of each type are given in Table 15, with information on bond lengths. The $S=\frac{3}{2}$ state can couple to a nearby $S=\frac{5}{2}$ state to give a new admixed intermediate state ($S=\frac{3}{2}, \frac{5}{2}$), which must not be viewed as a spin equilibrium.

Table 15 Spin States in Iron(III) Porphyrins

	$S=\frac{1}{2}$	$S=\frac{5}{2}$		$S=\frac{3}{2}$
Coordination number	6	5 or	6	6
	$[Fe(TPP)(HIm)_2]^+$ $[Fe(TPP)(CN)_2]^-$	$[Fe(TPP)Cl]^+$ $[Fe(TPP)]_2O$	$[Fe(TPP)(H_2O)_2]^+$ $[Fe(TPP)(DMSO)_2]^+$	$[Fe(TPP)C(CN)_3]_n$
$Fe-N_p$(Å)	1.97-2.00	2.06-2.087	2.045	1.995
Fe—axial (Å)	1.957-2.013		2.08-2.316	2.317

The coordination of strong field ligands such as imidazole leads to low-spin, six-coordinate porphyrins. Weaker ligands, such as Cl^- and N_3^-, give high-spin, five-coordinate porphyrins. As the field of the axial ligand decreases so the energy of the d_{z^2} orbital decreases, giving the sequence of spin states.

Occupation of the $d_{x^2-y^2}$ orbital in the high-spin porphyrin may result in an expanded porphinato core or in the movement of the iron out of the plane in five-coordinate complexes. In both cases values of Fe—Np are larger than the low-spin complex, as are the Fe-axial ligand bond lengths. The out-of-plane high-spin Fe^{III} is not prevented from being in-plane by its larger size.

The situation for Fe^{II} porphyrin is rather similar, with the existence of $S=0$, 1 and 2 states. The iron in $Fe(TPP)(THF)_2$ lies in the plane of the porphyrin.[647] This result is of considerable relevance to model systems for hemoglobin and the question of the trigger for the conformational change associated with the cooperative uptake of dioxygen. In this example the presence of a symmetrical weak axial field is the crucial factor. While this particular situation probably does not occur in any natural hemoprotein, these results demonstrate conclusively that high-spin Fe^{II} will fit into the porphyrin plane.

62.1.5.2 The Cytochromes

These are hemoproteins that catalyze electron transfer through the reversible change in oxidation state of the heme iron.[637] They are involved in the respiratory chain, and in a wide range of other processes such as photosynthesis and the nitrogen cycle. Over 50 cytochromes have been studied, notably cytochrome *c*, which is one of the best studied biological molecules. Bacteria in particular produce a wide range of cytochromes which currently are attracting much attention.

In some cases, heme centres are found in complex redox enzymes, in which a single protein molecule contains several redox centres. Thus, two hemes are found in (a) the cytochrome oxidases

of the aa_3 type, (b) the terminal oxidase *bd*, synthesized by *E. coli* when grown in the presence of formate, (c) the nitrite reductase of *Pseudomonas aeruginosa*, which contains cytochromes cd_1 and which is able to catalyze the four-electron reduction of dioxygen to water (the enzyme exists as a dimer), and (d) the cytochrome *c* peroxidase of *Ps. aeruginosa*. These examples will be considered in later sections. The present section deals with 'simple' electron-transfer reactions, where electron transfer is not coupled directly to an enzymatic reaction.

It should be noted that the *d* cytochromes involve a dihydroporphyrin, and so represent further examples of the chlorin prosthetic group.

62.1.5.2.1 Classification of cytochromes

Four different groups of cytochromes are defined. This classification is based upon the type of porphyrin present, and, for practical purposes, upon the spectra of the pyridine derivatives of the Fe^{III} form.

(1) Cytochromes *a*, in which the heme group contains a formyl side-chain.
(2) Cytochromes *b*, in which protoheme is the prosthetic group.
(3) Cytochromes *c*, which have covalent linkages between heme and protein.
(4) Cytochromes *d*, having the dihydroporphyrin group.

The position of the α-band lies in the ranges 580–590 (*a*), 555–560 (*b*), 548–552 (*c*) and 600–620 nm (*d*). The literature without doubt contains some cytochromes that are classified incorrectly. In addition there are cytochromes not covered by this classification.

Cytochromes of the *b* and *c* groups usually have two strong field axial ligands and are therefore low-spin. These will not bind small molecules. Cytochromes a_3 and *d*, in contrast, bind O_2 and act as terminal oxidases.

62.1.5.2.2 Cytochromes c

This discussion will consider cytochrome *c* first in some detail, and then survey current developments with respect to other *c*-type cytochromes (Table 16). In nearly all cases these cytochromes involve methionine and histidine residues as axial ligands.

Table 16 The *c* Cytochromes

Cytochrome	*Origin*	*MW*	E_0° (mV)	*Function*
c	Widespread	12 000–13 000	+255	Respiratory chain ($c_1 \rightarrow c \rightarrow aa_3$)
c_1	Widespread	37 000	+226	Respiratory chain ($b \rightarrow c_1 \rightarrow c$)
c_2	Photosynthetic, purple bacteria		+310, +340	Photosynthesis
c_3	*Desulfovibrio desulfuricans*	13 000 (4 hemes)	−205	Reduction of SO_4^{2-}
c_4	*A. vinelandii*	12 000	+300	
c_5	*A. vinelandii*	12 000	+320	
c'	Bacteria			Photosynthesis, denitrification
c_{552}	*Thermus thermophilus*	15 000	+230/190	
c_{552} (c_6, f)	*Euglena gracilis* chloroplasts	(2 hemes)		Photosynthesis
c_{550}	*Thiocapsa raseopersicina*	34 000		Reduction of S^{2-}
c_{551}	*Ps. aeruginosa*			
c_{553}	Photosynthetic bacteria			
c_{554}	*Alcaligenes faecalis*			Respiration, dentrification
c_{555}	*Chlorobium thiosulfatophilum*			
	Prostheochloris aestuarii			Photosynthesis

Various aspects of cytochrome *c* have been reviewed.[637,648–651] Cytochrome *c* is widely distributed, and has the apparently simple role of accepting an electron from cytochrome c_1 and transferring it to cytochrome oxidase. A major area of discussion is the pathway taken by the electron in its route from the surface of the protein to the heme and out again.

Cytochrome *c* from various sources consists of a single polypeptide chain of about a hundred amino acid residues. The protein is synthesized as apocytochrome *c* in the cell cytoplasm and then translocated across the outer mitochondrial membrane to its functional site on the cytoplasmic surface of the inner membrane.[652] The heme is added during or after transport.[653]

Horse heart cytochrome *c* has a molecular weight of 12 400 and 104 amino acid residues, with the heme group covalently bound in a crevice. One edge of the heme is exposed to the solvent. The axial ligands are His-18 and Met-80 groups. The structures of oxidized and reduced forms of tuna cytochrome *c* at high resolution are very similar,[654-657] suggesting that there is no conformational change during the redox reaction. This is supported by EXAFS measurements.[658] A similar situation holds for Fe^{II} and Fe^{III} bonito cytochrome *c*.[659] The basic folding pattern and hydrophobic heme environment of cytochrome *c* are also found in cytochrome *c*-551.[660] The folding patterns in cytochromes c_2 and *c*-550 are probably similar too. The structure of cytochrome *c*-555 from *Chlorobium thiosulfatophilum* has been determined.[661]

The only significant differences between the two redox forms of cytochrome *c* involve a buried water molecule, which is hydrogen bonded to Asn-52, Tyr-67 and Thr-78. The water molecule is further from the heme by 1.0 Å and the heme is deeper in the crevice by 0.15 Å in the reduced protein, giving a less polar environment.

The entry to the crevice is associated with positively charged lysine residues. This ring of positive charge is conserved in all the cytochromes *c* for which sequence data are available, and is commonly thought to represent a binding site for redox partners. Two channels lead from the surface to the heme group, and these have been suggested to be entry and exit pathways for the electron. However, it is now thought that the electron enters the protein through the exposed edge of the heme.

The involvement of the lysine residues has been explored. Thus, trifluoroacetylation of lysine residues 13, 55 and 99 has been carried out,[662] but only modification of residue 13 affects the reaction with cytochrome oxidase. Modification of lysine residues 13, 25, 27, 72 and 79 decreased the reaction rate of cytochrome *c* with cytochrome b_5. It is possible that the lysine groups in unmodified cytochrome *c* interact with the carboxylate groups in cytochrome b_5 (Asp-48, Glu-43, Glu-44 and Asp-60) and one of the heme propionate groups.[663] In general, such studies support the proposal that these lysine groups represent binding sites for redox partners of cytochrome *c*.

Another approach has been the preparation of fragments of cytochrome *c*, in which the heme group is bound to a portion of the protein, either by tryptic digestion or cyanogen bromide cleavage.

The use of cyanogen bromide gives two fragments with residues 1–65 and 66–104. The heme is covalently linked to the protein *via* Cys-14 and Cys-17. Thus fragment 1–65 contains the heme group, but does not provide the methionine axial ligand. These two fragments have been rejoined successfully, and also residues 1–65 with a synthetic sequence 66–104.[664] This approach allows the introduction of labelled or modified amino acid residues into the protein. A range of semisynthetic cytochromes have now been synthesized, in which attempts have been made to modify the highly conserved sequences, and so illuminate the likely role of these residues.[665-667]

Some small peptide–heme complexes have been prepared, including an undecapeptide (residues 11–21)[668-669] and an octapeptide (residues 14–21). These are useful models as they include the two cysteine residues that covalently link the heme to the peptide, and one of the axial ligands. The axial Met-80 residue is absent, but the position can be filled by methionine or by other ligands as required.[670] Work with several octapeptide complexes shows that the rates of outer-sphere electron transfer appear to be independent of the axial ligand, and faster than the reaction for cytochrome *c*. Other comparisons show that the orientation of the axial methionine in cytochrome *c* and the contacts between heme and protein are important controlling factors in the electronic structure of the heme. Aqua and hydroxo complexes of iron(III) octapeptide complexes are also useful models for studying spin equilibria in iron(III) hemoproteins.[671]

Some of the earlier work on simpler models can be discussed in more detail here. Much of this focuses on the role of Met-80 in controlling the redox potential of cytochrome *c*. Low-spin tetraphenylporphyrin complexes of Fe^{II} and Fe^{III} with thioether axial ligands have similar bond lengths (Fe—S = 2.34 and 2.33, 2.35 Å respectively).[672] Increase in Fe—S bond length on going to Fe^{III} is probably offset by the increased attraction of Fe^{III} for the ligand. However, the constancy of Fe—S bond length is important for rapid electron transfer, in accord with the application of the Franck–Condon principle. Models have also been prepared in which there is a porphyrin-linked imidazole and a thioether as axial ligands. Again there is a constant Fe—S distance.[640]

These authors have reported some interesting electrochemical studies on the imidazole/thioether complex and the bis(imidazole) complex. Substitution of one imidazole by the thioether results

in a change in the redox potential of +167 mV. However, the difference in redox potential between cytochrome c_3 (where there are two axial histidine residues) and cytochrome *c* is about 460 mV. If about 160 mV of this can be attributed to the replacement of histidine by methionine, then the remainder will be due to environmental effects. The destabilization of the Fe^{III} oxidation state in cytochrome *c* reflects its inability to delocalize the positive charge produced in the oxidation. The heme propionic acid side-chains of cytochrome *c* are buried in the protein, but this is not the case for cytochrome c_3. The ionization of the proprionic acid groups may then be important in controlling the redox potentials of the cytochromes.

The Fe—Met-80 link is also involved in the unfolding and refolding of the protein in reversible denaturation.[673] The last process in the unfolding and the first process during refolding are the disruption and formation of the Fe—Met-80 linkage respectively.

Other modifications to cytochrome *c* involve metal substitutions. A particularly well-known example involves the comparison of diamagnetic Co^{III} cytochrome *c* and Fe^{II} cytochrome *c* by NMR techniques. This showed the absence of conformational change, subsequently confirmed by the high resolution crystallographic studies. The nickel-, copper- and manganese-substituted cytochromes have all been studied. The reduced Mn^{II} cytochrome *c* was not oxidized by mammalian cytochrome oxidase aa_3.[674] It is possible that the manganese is five-coordinate, with the metal out of the plane towards His-18. The absence of the Fe—Met-80 link results in the absence of enzymatic activity. If this suggestion is correct, then the importance of the Met-80 group is emphasized.

The Sn^{IV} and Zn^{II} cytochromes *c* have been used in the study of the interaction of cytochrome *c* with cytochrome oxidase and mitochondria. The fluorescence yields of these two cytochromes fall on binding. Based on the known spectral overlap and quantum yield, it has been estimated that the distance between the porphyrin rings of cytochrome *c* and cytochrome *a* of cytochrome oxidase is 35 Å.[675] The decay mechanisms of the excited states of these substituted cytochromes have been studied.[676]

Electron transfer between the iron centre in cytochrome *c* and a transition metal bound at the periphery of the protein has been studied in cases where Cu^{II} [677] and the $Ru^{III}(NH_3)_5$ group[678] are bound to His-33. In the latter case, the Ru^{II}–cytochrome *c*(III) form can be generated by pulse radiolysis. The intramolecular transfer of an electron between Ru^{II} and Fe^{III} can be measured. This presents a useful model for electron transfer from the iron *via* the heme group and the protein.

Many kinetic studies have been carried out on the reactions of cytochrome *c*. This work, as is the case for other electron-transfer proteins, has followed two general courses. One approach involves the study of reactions of cytochrome *c* with inorganic and organic reagents and with isolated electron-transfer proteins. The second approach has involved the use of intact or partially disrupted mitochondrial or photosynthetic electron-transfer systems.

Examples of studies involving small molecules or ions as substrates include the reduction of ferricytochrome *c* by ascorbate[679] and Cr^{II},[680] and the oxidation of ferrocytochrome *c* (and c_{551}) by various Co^{III} complexes,[681,682] Cu^{II} [683] and ferricyanide.[684,685] These reactions in general proceed by an outer-sphere mechanism at the heme edge of cytochrome *c* which is exposed to the solvent. The most reactive oxidizing agent was ferricyanide, which was assumed to penetrate the protein surface through a cyanide ligand, possibly giving rise to Fe-CN-heme π-overlap. Reduction by the inner-sphere reagent Cr^{II} proceeds *via* a rate-determining cleavage of the Fe—Met linkage, followed by attack of the Cr^{II} aqua iron. Catalysis of this reaction by chloride ion results from the formation of an Fe-Cl-Cr transition state.[680]

The influence of added electrolytes on the reactivity of cytochrome *c* has been much studied. Thus, in the reduction of cytochrome *c* by ascorbate or dithionite[686] the limiting rate of opening of the heme crevice is suggested to be a salt-dependent phenomenon. Addition of 1 mol dm^{-3} NaCl imposes a more rigid structure on the molecule, and the rate of crevice opening falls by about 25%. Detailed ionic strength studies also allow calculation of protein charges, for example the ionic strength dependence of the rate of reduction by Fe^{II} EDTA of cytochrome *c* and cytochrome c_2 of *Rhodespirillum rubrum* gives values[687] of the protein charges of +10 and +2.3 respectively. This compares very well with the values of +9 and +3 for the overall charge on the proteins calculated on the numbers of acidic and basic amino acid residues.

The binding of small inorganic ions such as $[Fe(CN)_6]^{3-}$ and $[Cr(en)_3]^{3+}$ can be used to explore binding sites on electron-transfer proteins. Thus redox inactive $[Cr(en)_3]^{3+}$ inhibits the oxidation of cytochrome b_5 with $[Co(NH_3)_6]^{3+}$ and other oxidizing agents, and also blocks association with cytochrome *c*. The reaction of cytochrome b_5 with the oxidants occurs by a mechanism involving association of the reactants prior to electron transfer. The reaction may then be inhibited by redox

complexes that bind at the same site on the protein surface. However, the fact that $[Cr(en)_3]^{3+}$ also blocks the association with cytochrome *c* implies that cytochrome *c* (positive charge 9) binds at the same negatively charged site on cytochrome b_5 as the inorganic complex.[688] A procedure for estimating the local effective charge on a protein surface from association constants for surface reactions of metalloproteins with inorganic complexes has been developed.[689]

The electrochemistry of cytochrome *c* is attracting much attention,[690] in particular the development of electrodes for cytochrome *c*, which either have a redox mediator bound to the surface, or utilize a solution mediator. Examples are a platinum gauze electrode functionalized with 2,3,4,5-tetramethyl-1-(dichlorosilyl)methyl[2]ferrocenophane,[691] and 4,4′-bipyridyl, which serves as a bridge between cytochrome *c* and the electrode.[692]

Some particularly interesting cytochromes are found in bacteria. Cytochrome *c′* constitutes a class of high-spin cytochromes which are widely distributed in photosynthetic and denitrifying bacteria,[693] and which are suggested to be the largest and most widespread class of bacterial cytochromes known,[694] although no specific role has been ascribed to them. They have attracted attention because they show properties similar to functionally different classes of hemoproteins. Thus, the visible spectrum at neutral pH resembles that of myoglobin rather than cytochrome *c*. However, the cytochromes *c′* may be autoxidized, and have other properties similar to low-spin cytochrome *c*. X-Ray studies indicate that the cytochromes *c′* represent a unique class of *c* cytochromes, whose overall tertiary structure resembles neither the mitochondrial cytochrome *c* or hemoglobin.[695] The heme iron is five-coordinate with a solvent-exposed histidine as the axial ligand.

Five spectroscopically distinguishable forms have been observed for cytochrome *c′* from *Rhodospirillum rubrum*, two in the reduced state and three in the oxidized state. These exist under different conditions of pH. However, three oxidized forms have been observed in the pH range 6–9.5 by the use of Mössbauer spectroscopy. These are all high-spin.[696] In addition, a low-spin oxidized form has been found at pH values greater than 12, suggesting there are four oxidized forms. NMR and other studies suggest that the low-spin, high pH form is a monomer, and that high-spin forms are dimeric.[697] The magnetochemistry of these forms has been in dispute.[598,698]

Cytochromes *c′* bind NO and CO at physiological pH values, apparently binding two CO molecules at each heme.[699] More recently, the binding of ethyl isocyanide to a number of cytochromes *c′* has been investigated.[700] Binding constants show more than a 1000-fold variation over the cytochromes *c′* studied. The lack of affinity for a sixth ligand displayed by cytochromes *c′* (compared to hemoglobin) has been attributed to a weaker axial imidazole ligand field or to steric hindrance at the sixth position. However, there is no correlation between binding constants for ethyl isocyanide and for CO with different cytochromes *c′*. This has been interpreted to mean that the lack of affinity is due to steric hindrance rather than to electronic effects. Indeed the ratios K^{CO}/K^{EIC} for certain of the cytochromes *c′* are similar to those found for model systems with built-in steric effects. The X-ray data suggest that residues Met-26, Leu-19 and Trp-86 block the sixth site in *Rs. molischianum* cytochrome *c′*.

Cytochrome c_3 is a multiheme protein, which has a very negative redox potential (Table 16), and which has been isolated from the sulfate-reducing bacteria of *Desulfovibrio* species. Cytochrome c_3 accepts electrons from hydrogenase (the initial electron donor is H_2) and transfers them *via* other redox centres to the final electron acceptor (SO_4^{2-}). Cytochrome c_3 has four *c*-type hemes with histidine axial ligands.[701] Electron transfer within cytochrome c_3 is controlled by inter- and intra-molecular heme–heme interactions. Direct electron transfer between some of the redox centres is proposed, as a result of close interaction between pyrrole rings of neighbouring heme groups. The folding of the protein results in interactions between porphyrins and aromatic side-chains or cysteine residues, and leads to the sequence: heme 1 → Phe-88 → heme 4 → Cys-61 → heme 3 → Phe-34 → heme 2 → Cys-114 → heme 1 · · ·.[702] Kinetic studies[703] indicate that the four hemes behave as equivalent pairs in terms of intramolecular electron transfer, in contrast to NMR evidence.

There are a number of low molecular weight cytochromes (with 84–86 amino acid residues) which appear to form a subclassification of the cytochrome *c* family. Cytochrome c_{554} from *Alcaligenes faecalis* donates electrons to a soluble nitrite reductase during denitrification and presumably to a cytochrome oxidase during aerobic respiration. It has 86 amino acid residues, and its composition is similar to cytochrome c_{551} from *Pseudomonas aeruginosa*,[660] while there are also similarities with cytochrome c_{553} from photosynthetic bacteria. Detailed NMR studies of c_{554}[704] and c_{553}[705] are available. The electron-transfer rate between Fe^{II} and Fe^{III} forms of c_{554} is estimated to be about 3×10^8 dm^3 mol^{-1} s^{-1}, which is the largest self-exchange rate yet observed for a cytochrome.

Cytochrome c_{552} from *Euglena gracilis* (also known as cytochrome *f* or c_6) contains 87 amino acid residues, two hemes and one flavin per molecule.[693] NMR studies[706] indicate that the chirality of the axial methionine is similar to that of cytochrome *c* but different from cytochrome c_{551}. Rapid intramolecular transport has been demonstrated by the use of pulsed laser excitation, and the measurement of reduction kinetics. Both flavin and heme groups are reduced simultaneously on a multisecond time scale, with the transient formation of a protein-bound flavin anion radical.[707]

The denaturation of cytochromes c_{552} has been much studied.[708] Cytochrome c_{552} (*f*) is suggested to bind to its natural redox partner plastocyanin at a negatively charged area incorporating residues 42–45 of plastocyanin.[709] A cytochrome *f* from a cyanobacterium has 85 residues.[710] The methodology for extracting cytochromes c_{552}, $c_{555,549}$, c_1aa_3 and aa_3 from the thermophilic aerobe *Thermus thermophilus* has been described.[711]

62.1.5.2.3 Cytochromes b

Cytochromes of this group are widely distributed. Examples are listed in Table 17. Cytochrome *b* is a component of the respiratory chain in many aerobic organisms, but only as a complex bc_1 in mitochondria (and 'b_6f' in chloroplasts). The separation of bc_1 may involve a modification of cytochrome *b*. Amino acid sequences of a number of mitochondrial cytochromes *b* are available.[712]

Table 17 The *b* Cytochromes

Cytochrome	*Origin*	*MW*	E_0' (mV)	*Function*
b	Widespread (mitochondria, bacteria)	(c_1b)	—	Respiratory chain
b_1	Bacteria	13 000?	+250	Respiratory chain, nitrate reductase
b_2	Yeast	Tetramer (235 000)		Electron carrier Also contains FMN
b_3	Plant microsomes	40 000	+40	
b_5	Animal microsomes	12 000	+20	Electron carrier between b_5 reductase and cyt *c*
b_{562}	*E. coli*	12 000		
b_6	Chloroplasts		−60	
b_{559}	Chloroplasts		+360	
b_7			−30	

Cytochrome *b* spans the membrane,[713] and contains two protohemes. The nature of the axial ligands in cytochrome *b* is not known with certainty. Current views support either two imidazoles or an imidazole and an amino group. The residues of the various cytochromes *b* contain six invariant histidines and two lysines. Four of the histidines are found in two protein segments that span the membrane. In each, two histidines are separated by 13 residues. On a helical surface these will then be located almost exactly above each other on the same side of the helix. This allows a proposal that cytochrome *b* does have two axial imidazole ligands, and that the two protohemes link the two protein segments that span the membrane. This model results in the Fe–Fe distance being about 20 Å with each iron centre being about 10 Å inside the membrane, and accounts for the known perpendicular orientation of the heme planes with respect to the membrane plane (Figure 29).[712] Chloroplast cytochrome b_6 is smaller than the mitochondrial protein, and appears to correspond to the N-terminal portion of the mitochondrial cytochrome *b*. The proposed heme-binding histidines are present in cytochrome b_6.

Cytochrome b_5 was first isolated from rat liver microsomes. It is a membrane-bound protein which is solubilized readily and is relatively stable. It participates in at least three processes involving electron transfer, namely stearyl-CoA desaturation, reduction of cytochrome P-450 and reduction of methemoglobin. It contains 93 amino acid residues and one heme group, the iron having two histidine residues as axial ligands. The 83 residue cytochrome produced by trypsin hydrolysis has similar catalytic properties. Cytochrome b_5 does not combine with carbon monoxide, cyanide or azide. It is autoxidized slightly. The structure of cytochrome b_5 has been reported.[714] A study of the ionic strength dependence at pH 7 of the rate of reduction of cytochrome b_5 by $Fe(EDTA)^{2-}$ gives a charge on the protein of −14.2.[715] The self-exchange rate is similar to that of cytochromes *c* and c_{551}.

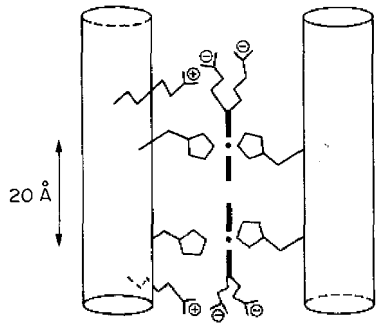


Figure 29 Possible heme-binding sites in cytochrome *b* (reproduced with permission from *FEBS Lett.*, 1984, **166**, 367)

The cytochrome b_{562} from *Escherichia coli* involves histidine and methionine axial ligands as shown by crystallographic studies.[716]

The roles of cytochromes b_{563}[717] and b_2 in electron transfer have been investigated. Cytochrome b_2 contains heme and flavin centres, and transfers electrons to cytochrome *c* after abstracting hydrogen from the substrate. Cytochrome *c* can withdraw an electron from the reduced three-electron donor flavo-cytochrome b_2 only at the heme site. The donor heme site is then supplied with an electron from the flavin site, so that two further molecules of cytochrome *c* may ultimately be reduced.[718]

62.1.5.2.4 Cytochromes a and d

Cytochrome oxidase (cytochrome aa_3) represents the most important cytochrome of the *a* class. This is the terminal oxidase used in animals, plants, yeasts, algae and some bacteria. It contains two copper centres, giving four redox groups in total. This oxidase is discussed with other cytochromes that have a terminal oxidase function in Sections 62.1.12.4 and 62.1.12.5. These are cytochromes *o*, *d* and cd_1. The oxidases bd[719] and a_1 are not included in that discussion. The situation regarding cytochrome a_1 has been confused, partly due to uncertainty in the definition of this cytochrome. In some respects, the properties of cytochrome a_1 resemble those of mitochondrial and bacterial aa_3. It functions as a terminal oxidase in some bacteria,[720] but its role in *E. coli* is unknown. A soluble fraction from disrupted *E. coli* cells grown anaerobically on glycerol and fumarate contains a hemoprotein similar to cytochrome a_1, which has catalase and peroxidase activity.[721]

Several of these cytochromes use nitrogen compounds as electron acceptors. Cytochrome cd_1 from *Pseudomonas aeruginosa* is a greenish-brown soluble enzyme which contains one *c* and one chlorin (d_1) heme in each of two subunits of 63 000 molecular weight. The presence of four redox centres is appropriate for the efficient catalysis of the four-electron reduction of dioxygen to water. It appears, however, that its physiological role may be the reduction of nitrite to NO. Kinetic studies on the anaerobic reduction of cd_1 by $Fe(EDTA)^{2-}$ have focused attention on electron transfer between the heme groups in the enzyme.[722]

The spectrum of reduced cytochrome *d* in *E. coli* membranes is affected by added nitrate. The new spectrum formed may be that of a nitrosyl complex. Similar but faster changes were brought about by nitrite, trioxodinitrate or NO.[723] The nitrate may be reduced to nitrite by a nitrate reductase in a slow step, followed by further reduction by reduced *d*. These nitrate-induced spectral changes in cytochrome *d* had been attributed previously to Ag^+ added as silver nitrate.

62.1.5.2.5 Cytochrome interactions in the respiratory chain

The purification and characterization of individual cytochromes (simple or complex) and other redox centres in electron-transfer chains leads to a study of their interactions with each other, with the ultimate objective of reconstituting parts of the chain. Approaches to this problem will be illustrated[724] with reference to the reaction of cytochrome *c* with ubiquinol cytochrome *c* reductase (complex III, cytochrome bc_1) and cytochrome oxidase (complex IV) as shown in equation (21).

$$\text{ubiquinol cytochrome } c \text{ reductase (cytochrome } bc_1\text{)} \rightarrow \text{cytochrome } c \rightarrow \text{cytochrome oxidase} \rightarrow O_2 \quad (21)$$

The importance of lysine groups around the heme-binding crevice in cytochrome *c* as binding groups for its redox partners has already been stressed, and has been demonstrated by chemical modification experiments.[662] The question of whether there are different sites for binding of complex III and complex IV is not fully resolved. However, the same lysine residues are shielded from acetylation by complexing cytochrome *c* with either of these complexes,[725] implying that they bind at the same site and that therefore entry and exit of the electron follows the same route.

The complex III site on cytochrome *c* is also used by cytochrome b_5[663] and other redox proteins such as cytochrome *c* peroxidase.[726] The availability of structural information has allowed computer fitting of cytochrome *c*–cytochrome b_5 and cytochrome *c*–cytochrome *c* peroxidase structures, and the demonstration of negatively charged areas on the cytochrome b_5 and cytochrome *c* peroxidase that complement the positively charged areas on cytochrome *c*.[727,728] The interaction between cytochromes *c* and b_5 at these regions will bring the two hemes to within 8.5 Å of each other and in parallel orientation. In the case of cytochrome *c* peroxidase and cytochrome *c*, the hemes will be parallel and 16.5 Å apart. It seems reasonable that cytochrome c_1 of complex III and the appropriate subunit of cytochrome oxidase will have a negatively charged area to allow interaction with this site on cytochrome *c*.

If entry and exit of electrons to and from cytochrome *c* involves the same site, then cytochrome *c* must be able to interact reversibly with both redox partners and to move between them. The rate of rotational diffusion of cytochrome *c* oxidase in vesicles is independent of the presence of complex III and cytochrome *c*. This suggests that a stable aggregate between these three components is not formed and, therefore, that cytochrome *c* shuttles between complex III and cytochrome oxidase by lateral diffusion along the membrane.[729] A mitochondrial protein has been purified which is essential for the formation of the cytochrome c_1–*c* complex. This is suggested to serve as a 'hinge protein'.[730] Complex III contains a single binding site for cytochrome *c*. This has been localized by chemical crosslinking to cytochrome c_1.[731] Similarly, two sites for cytochrome *c* on cytochrome oxidase have been identified by crosslinking experiments. It is suggested[724] that reduced cytochrome *c* binds to the low affinity site on cytochrome oxidase, causing release of oxidized cytochrome *c* from the high affinity site. Reduced cytochrome *c* in the low affinity site then transfers into the high affinity site and gives up its electron to cytochrome oxidase. The oxidized cytochrome *c* is then replaced by a reduced cytochrome *c* as before.

62.1.5.3 Chlorins and Isobacteriochlorins

Several heme enzymes are iron complexes of chlorins or isobacteriochlorins. Porphyrins that contain two reducing equivalents (hydrogen atoms or alkyl groups) across the vicinal C_b atoms of a single pyrrole ring are called chlorins. Cytochromes *d* and d_1 discussed in Sections 62.1.5.2 and 62.1.12.5 are chlorins. Porphyrins with two adjacent reduced pyrrole group rings are isobacteriochlorins. An example is siroheme, the heme prosthetic group of the sulfite and nitrite reductases, which has eight carboxylate side chains (Figure 2). Both enzymes catalyze a six-electron reduction (equations 22 and 23).

$$NO_2^- + 7H^+ + 6e^- \rightarrow NH_3 + 2H_2O \quad (22)$$

$$SO_3^{2-} + 8H^+ + 6e^- \rightarrow H_2S + 3H_2O \quad (23)$$

The structure of iron(II) octaethylchlorin shows the iron and four nitrogen atoms to be rigorously planar, but the rest of the chlorin macrocycle to be significantly S_4 ruffled.[732] Hydroporphyrins intrinsically have larger cores than porphyrins, but the distortion from planarity leads to a reduction in core size and shorter metal–nitrogen distances. The enhanced ability of hydroporphyrins to undergo distortion so as to adjust their core size in response to the size of the metal may be responsible for the differences between iron porphyrins and hydroporphyrins.[733]

It is noteworthy that siroheme is present in the enzymes responsible for catalyzing two out of only three known six-electron processes, and accordingly it is of great interest to try and identify any feature in siroheme that makes it particularly suitable for the mediation of multielectron transfer. A comparison of octaethylporphyrin, octaethylchlorin and octaethylisobacteriochlorin complexes of iron shows that redox potentials and ν_{CO} of Fe(P)L(CO) and Fe(P)L$(CO)_2$ were nearly independent of the porphyrin. The property that was most dependent upon the macrocycle structure was the potential for ring-based oxidation which increased in the order OEiBC < OEC < OEP.[734]

There is also much interest in the biosynthesis of siroheme and its relationship to the corrinoid ring system.[735]

The E_0' values for siroheme in *E. coli* sulfite reductase and spinach nitrite reductase are −345 and −50 mV respectively, compatible with direct roles for siroheme in the reductions. Treatment of sulfite reductase with cyanide or carbon monoxide prevents binding of sulfite. Several other arguments indicate that the substrate may bind to the siroheme at or close to the iron centre.

62.1.5.4 The Iron–Sulfur Proteins

These are involved in a wide range of electron-transfer processes and in certain oxidation-reduction enzymes, whose function is central to such important processes as the nitrogen cycle, photosynthesis, electron transfer in mitochondria and carbon dioxide fixation. The iron–sulfur proteins display a wide range of redox potentials, from +350 mV in photosynthetic bacteria to −600 mV in chloroplasts.

These proteins contain iron bound by sulfur ligands, namely cysteinyl residues from the peptide, and, with the exception of rubredoxin, inorganic 'acid-labile' sulfide. The iron–sulfur groups fall into a number of structural types. Rubredoxin contains one iron bound by four cysteinyl residues, while [2Fe-2S] and [4Fe-4S] clusters are well characterized. More recently, there has been great interest in three-iron proteins [3Fe-*n*S], for which a number of important questions remain to be answered. Excellent inorganic analogues are available for these iron–sulfur clusters (with the exception of the three-iron cluster), and the study of the structures and redox properties of these inorganic compounds has contributed substantially to our understanding of iron–sulfur proteins.

Many reviews are available. Older work is well summarized in a series on the iron–sulfur proteins,[736] while reviews are available on general aspects,[737,738] structural features,[739] bacterial iron–sulfur proteins[740] and three-iron clusters.[741]

This account will deal in turn with structural features of the one-iron, two-iron, four-iron and three-iron proteins, and also with the most important topic of interconversion between the three-iron and four-iron clusters. Model compounds will be described briefly. Finally, kinetic studies and the role of iron–sulfur proteins in complex enzymes will be discussed.

Iron–molybdenum–sulfur clusters will be considered in Section 62.1.14, which deals with aspects of the nitrogen cycle.

62.1.5.4.1 Rubredoxin

The rubredoxins are the simplest type of iron–sulfur protein. The first example was isolated from *Clostridium pasteurianum*, and others have been found in a number of organisms. The iron is bound by four cysteinyl ligands in an approximately tetrahedral stereochemistry, with four equivalent Fe—S bonds, with average bond length 2.267 ± 0.003 Å from EXAFS measurements.[742] The protein from *Desulfovibrio gigas* has a similar structure with average Fe—S bond length 2.29 Å (Figure 30). The oxidized and reduced forms of rubredoxin have been well characterized by spectroscopic techniques. The NMR method gives magnetic moments of 5.85 and 5.05 BM respectively, implying high-spin Fe^{III} and Fe^{II}, while the ^5E–^5F transition for high-spin Fe^{II} in

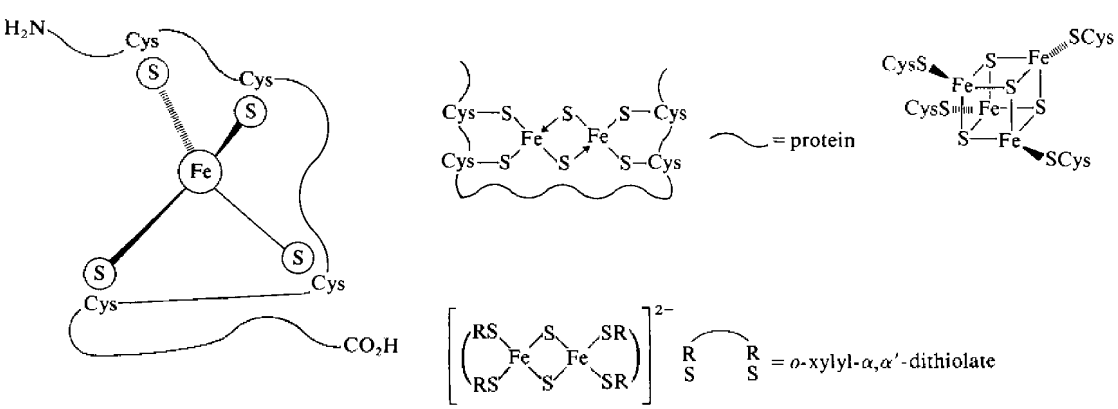


Figure 30 Structures of the one-iron, two-iron and four-iron centres in the iron-sulfur proteins and of a model compound

a tetrahedral field occurs at 6250 cm^{-1} (the $10Dq$ value for the cysteine ligand). The Raman spectrum of crystalline rubredoxin shows ν_{Fe-S} modes at 365 and 311 cm^{-1}. These occur in solutions of rubredoxin at 368 and 314 cm^{-1}. This shows that the geometry is tetrahedral, and confirms the maintenance of the geometry around the metal in the crystalline and solution states.

The molecular weights of rubredoxin from different sources are about 6000. The proteins from *D. vulgaris* and *D. gigas* have 37 of their 52 and 54 amino acid residues in common, but only 12 residues identical with rubredoxin from other bacteria. These 12 residues are concerned mainly with the iron-binding sites.

Two unusual rubredoxins are known at present, from *D. gigas* and *Pseudomonas oleovorans*. Both have two iron centres but differ from each other. The rubredoxin from *D. gigas* (desulforedoxin) has a molecular weight of 7900, with no acid labile sulfide and eight cysteine residues.[744] The electronic spectrum is different from that of the two-iron rubredoxin from *P. oleovorans* in that it is not simply the addition of two spectra of one-iron rubredoxins. These additional features have led to the suggestion that the two iron centres interact.

Ps. oleovorans contains two sites for iron, which do not interact. Data from the cyanogen bromide-cleaved enzyme suggest that each binding site is composed of cysteine residues from only one end of the molecule. Iron bound at the N-terminal site is very labile, so that rubredoxin as isolated from this organism only contains one iron, which is bound at the C-terminal site. Reconstitution of aporubredoxin with two mol of iron gives the 2Fe rubredoxin, but the N-terminal iron is lost easily in solution at room temperature.[745] The apoprotein also took up two Co^{II} ions. Spectroscopic data were consistent with the Co^{II} being present in a rubredoxin-type site, showing d-d and CT spectra similar to those found for the model compound $[Co(S_2\text{-}o\text{-}xyl)_2]^{2-}$. The cobalt protein was more stable than the native protein towards denaturation and the loss of metal, and carried out the physiological function of the native rubredoxin, although less effectively.

The *Ps. oleovorans* rubredoxin is part of an enzyme complex that catalyzes hydroxylation of the terminal methyl group of alkanes and fatty acids. It also readily converts terminal alkenes to the corresponding 1,2-oxides. Rubredoxins from anaerobic organisms accept electrons from the *Ps. oleovorans* reductase and have metal-binding sites and redox potentials analogous to those of *Ps. oleovorans* rubredoxin. However, they are unable to catalyze hydroxylation in the *Ps. oleovorans* system. One difference from 'anaerobic' rubredoxins is that *Ps. oleovorans* rubredoxin has a cluster of five cysteinyl residues near each terminus, so that a single uncoordinated SH group is available near each metal-binding site. The possibility that the extra sulfhydryl groups play a role in the function of the protein has been considered in some elegant experiments. In these the dicobalt(II) rubredoxin was formed. The greater stability of this species allowed selective modification of the free SH group with iodoacetamide. Removal of cobalt and restoration of iron thus gave rubredoxin with iron at the metal site and with the extra sulfhydryl groups chemically blocked. However, the modified protein was still able to catalyze epoxidation with lowered activity, suggesting that the extra sulfhydryl groups are not directly involved in catalysis.[746]

Attempts have been made to model the $[Fe^{III}(S\text{-}cys)_4]$ unit of rubredoxins. One problem is that the iron centre polymerizes rapidly and undergoes internal redox reactions to give Fe^{II} and RSSR groups. This does not favour the formation of complexes with four simple monodentate thiolate ligands. Examples reported include the use of bidentate[747] and sterically hindered ligands (2,3,5,6-tetramethylbenzenethiolate),[748] although a route to iron(III) complexes with less sterically hindered ligands has been established.[749] The compound $(NEt_4)[Fe(SPh)_4]$, prepared by this route, has average Fe—S distances of 2.296 Å, about 0.06 Å shorter than the Fe—S distances in the more easily prepared analogue, $(PPh_4)_2[Fe^{II}(SPh)_4]$.[750] Cysteine-containing peptides react with iron(III) chloride in DMSO and the presence of base to give an analogue of rubredoxin. Addition of aqueous sodium sulfide results in conversion to a [4Fe–4S] analogue.[751]

These tetrathiolate complexes have been of some utility in the controlled preparation of clusters with two, three, four and six iron atoms.[752] The six-iron cluster may not appear at present to be of biological significance, but it is not possible to preclude the possibility that it may exist naturally. The hexanuclear cluster $[Fe_6S_9(SBu^t)_2]^{4-}$ contains three types of bridging sulfur atom.[753] Each iron atom has a distorted FeS_4 coordination, and the structure is made up of eight fused Fe_2S_2 groups. Other hexanuclear iron centres are known.[754,755]

62.1.5.4.2 [2Fe–2S] proteins

These proteins have been isolated from animal, plant and bacterial sources, but mainly from photosynthetic organisms (Table 18). The structure shown in Figure 30 has long been accepted

Table 18 Some Iron-Sulfur Proteins

Cluster (name)	*Source*	*MW*	E_m(mV)
No sulfide			
1Fe (rubredoxin)	*Clostridium pasteurianum*	6 000	−570
1Fe (rubredoxin)	*Cl. formicoaceticum*	5 800	
1Fe (rubredoxin)	*Peptococcus aerogenes*		
1Fe (rubredoxin)	*Desulfovibrio desulfuricans*	6 000	
2Fe (desulforedoxin)	*D. gigas*	7 900	−35
2Fe	*Pseudomonas oleovorans*		
[*2Fe-2S*]			
Rieske protein	Mitochondrial complex III	30 000	+150 → +330
Rieske protein	*Thermus thermophilus*		
Adrenodoxin	Pig adrenals	13 000	+280
Putidaredoxin	*Ps. putida*	12 500	−240
	Azotobacter	21 000	−270
	Cl. pasteurianum	25 000	−300
	Escherichia coli	12 600	−360
	Spirulina platensis	10 648	−381
	Spinach	11 000	−390
	Halobacterium	14 000	−345
[*4Fe-4S*]			
Fd: $[C]^{2+/1+}$	*Bacillus stearothermophilus*	8 000	−280
	B. polymyxa	9 000	−422
	D. desulfuricans	6 000	−330
	Cl. thermoaceticum	7 300	
	Cl. formicoaceticum	6 000	
	Rhodospirillum rubrum	14 500	−430
HiPIP: $[C]^{3+/2+}$	*Chromatium vinosum*	10 000	+350
	Paracoccus		+360
	Rhodopseudomonas gelatinosa		
2 [*4Fe-4S*]			
	Cl. acidiurici	6 000	−434
	Cl. pasteurianum	6 000	−395
	Chromatium vinosum	13 000	−490
	Peptococcus aerogenes	6 000	−400
[*3Fe-4S*]			
FdII	*D. gigas*	24 000	−130
	Hydrogenase (D. desulfuricans)		
	Succinate-ubiquinone oxidoreductase (complex II)		
	Aconitase (inactive)	83 000	0
	B. stearothermophilus		0
[*7Fe-nS*]			
[4Fe-4S], [3Fe-3S]	*Azotobacter vinelandii*	14 500	+340, −420
[4Fe-4S], [3Fe-*n*S]	*T. thermophilus*		−530, −250
[4Fe-4S], [3Fe-*n*S]	*Mycobacterium smegmatis*		
[4Fe-4S], [3Fe-*n*S]	*Ps. ovalis*		−600
[4Fe-4S], [3Fe-*n*S]	*T. aquaticus*		
[4Fe-4S], [3Fe-*n*S]	*A. croococcum*		
[4Fe-4S], [3Fe-4S]	*Cl. pasteurianum* ($[Fe(CN)_6]^{3-}$ treatment)		

on the basis of spectroscopic evidence on the proteins and chemical analogues, for which the structures are known. Each iron atom is bound to two cysteinyl sulfur atoms and to two common bridging sulfide ions, and has a distorted tetrahedral geometry. It is only comparatively recently that an X-ray structure (at 2.5 Å resolution) of a two-iron protein has been reported, namely for a chloroplast ferredoxin from the blue-green alga *Spirulina platensis*.[756] This confirms the general structure in Figure 30, and involves four cysteine ligands, residues 41, 46, 49 and 79.

The primary structures of at least 28 [2Fe-2S] proteins have been determined.[757] Twenty-six of these have been isolated from plants or algae. The remaining two are from halobacteria, and have about 20 extra residues at the N-terminus and about five extra residues at the C-terminus in comparison with the plant-type proteins. These structural differences will account for their physiological differences. Thus, the halobacterial ferredoxin does not form a complex with ferredoxin-NADP reductase, in contrast with plant-type [2Fe-2S] ferredoxins.

The oxidized [2Fe-2S] protein is diamagnetic and ESR inactive, while the reduced form is paramagnetic, and usually has a $g = 1.94$ ESR signal. The diamagnetism of the oxidized form

results from antiferromagnetic interaction between the two high-spin ($S=\frac{5}{2}$) Fe^{III} centres.[758] On reduction, one electron is accepted, giving an $S=\frac{1}{2}$ dimer, but it appears from Mössbauer and ENDOR spectroscopy that localized Fe^{II} and Fe^{III} oxidation states are present. Mössbauer spectra measured in magnetic fields show conclusively that antiferromagnetic coupling takes place in the reduced form, and that the Fe^{III} centre has a relatively low symmetry and strong Fe—S covalency.

Some excellent model compounds are available. Potassium dithioferrate, $KFeS_2$, is a linear polymer of iron(III) centres bridged by two sulfide groups. The Fe—Fe distance is 2.7 Å, a value that implies some Fe—Fe direct interaction. $KFeS_2$ is an antiferromagnet. ESR studies confirm the delocalization of spin on to the sulfur centres. A number of sulfide-bridged binuclear complexes of iron are known, including $[Fe_2S_2(S_2\text{-}o\text{-xyl})_2]^{2-}$ shown in Figure 30.[759] Other examples are known with alternative terminal ligands such as halide.[760,752] Models for the two-iron site $[Fe_2S_2(SPh)_4]^{2-}$ have also been prepared from aqueous-based media.[761]

An unusual [2Fe-2S] ferredoxin with unique spectroscopic properties exists in association with cytochromes *b* and c_1 and is involved in respiratory electron transport in mitochondria, chloroplasts and certain bacteria. When isolated, the complex contains two *b* hemes, one c_1 heme and the 2Fe-2S protein. The 2Fe-2S protein from the bc_1 complex (Sections 62.1.5.2.3 and 62.1.5.2.5) was purified from bovine mitochondria by Rieske *et al.*,[762] and is referred to as the 'Rieske' iron-sulfur protein. The properties of this protein have been reviewed[763] and its topography in mitochondrial ubiquinol-cytochrome *c* reductase has been described.[764] They have high redox potentials in the range +150–330 mV.

The Rieske protein from *Thermus thermophilus* has been purified,[765] and demonstrated to contain two identical [2Fe-2S] clusters. It is suggested that each [2Fe-2S] cluster is coordinated by at most two cysteine residues. The Mössbauer spectra of the reduced protein suggest that the non-cysteine ligands are coordinated to the site that becomes reduced to Fe^{II} on reduction of the protein. The non-cysteine ligands are suggested to be imidazole, phenolate, hydroxylate or carboxylate. Model compounds have now been prepared having oxygen- and nitrogen-donor terminal ligands[766] (biphenolate, *p*-cresolate and pyrrolate anions). While these compounds have similar electronic and Mössbauer spectral characteristics to the Rieske proteins, substitution for sulfur ligands by either oxygen or nitrogen ligands results in a more negative redox potential rather than a more positive one. In the case of the four-iron clusters $[Fe_4S_4(SR)4]^{2-}$, a positive shift in the redox potentials occurs only when the thiolate ligands are displaced by carboxylate ligands.[767] This suggests that it is necessary to have carboxylate ligands as the non-cysteine ligands in the Rieske proteins to account for their high redox potentials.

62.1.5.4.3 [4Fe–4S] proteins

A number of proteins contain one or two [4Fe-4S] clusters, in which iron and sulfide are arranged in a distorted cubic structure, with each iron linked to the protein *via* cysteine residues (Figure 30). Each cluster undergoes a one-electron redox reaction. *Clostridium* or *Peptococcus aerogenes* ferredoxin contains two Fe_4S_4 cubes separated from each other by 12 Å and has a redox potential of −400 mV, while high potential iron protein (HiPIP) from *Chromatium vinosum* has a redox potential of +350 mV. The structures of these two cubes are very similar, and it is intriguing to consider the vastly different redox potentials associated with them. The long standing proposal[768] that three overall oxidation states of the cluster are physiologically significant is now generally accepted. These are shown in equation (24). The HiPIP protein cycles between the upper two oxidation states and the ferredoxin (Fd) between the lower two. The intermediate state will be common to HiPIP and Fd, and will be diamagnetic due to the presence of antiferromagnetic interactions between the iron centres and an even number of electrons in total. The other two oxidation states are paramagnetic.

$$\underset{\substack{Fe^{2+},3Fe^{3+}\\ \text{paramagnetic}\\ \text{(superoxidized Fd)}\\ \text{oxidized HiPIP}}}{[Fe_4S_4(S\text{-}Cys)_4]^{-}} \underset{-e^-}{\overset{e^-}{\rightleftharpoons}} \underset{\substack{2Fe^{2+},2Fe^{2+}\\ \text{diamagnetic}\\ \text{oxidized Fd}\\ \text{reduced HiPIP}}}{[Fe_4S_4(S\text{-}Cys)_4]^{2-}} \underset{-e^-}{\overset{e^-}{\rightleftharpoons}} \underset{\substack{3Fe^{2+},Fe^{3+}\\ \text{paramagnetic}\\ \text{reduced Fd}\\ \text{(super-reduced HiPIP)}}}{[Fe_4S_4(S\text{-}Cys)_4]^{3-}} \qquad (24)$$

As the $HiPIP_{red}$ and Fd_{ox} forms are experimentally indistinguishable in terms of the cluster, it is clear that their redox behaviour must be controlled by the protein, which prevents further oxidation of Fd_{ox} or further reduction of $HiPIP_{red}$. No single iron-sulfur protein is known which

will undergo reversible redox reactions between all three oxidation levels of the cube. However, HiPIP can be reduced to the super-reduced form in the presence of 80% DMSO, a reagent which causes the protein to unfold. It has also been proposed that the treatment of oxidized Fd from *Clostridium pasteurianum* with ferricyanide gives the superoxidized form. However, it is now known that this involves the conversion of the [4Fe-4S] cluster into a three-iron protein, as will be discussed in the following section.

Some detailed comparisons of the protein environments around the HiPIP and Fd clusters have been made.[769,770] It is noteworthy that the HiPIP cluster is more deeply buried (about 4.5 Å) than is the case for the clusters in the other iron-sulfur proteins. All iron-sulfur proteins for which structural data are available, with the exception of the three-iron protein from *Azotobacter vinelandii*, have hydrogen bonding between the cysteine sulfur in the iron-sulfur cluster and the backbone peptide link. It appears that there is an approximate correlation between the number of NH···S hydrogen bonds in the environment of a cluster and its redox potential. In HiPIP, these hydrogen bonds become more linear and shorten on reduction of the cluster. It is possible, therefore, that the oxidation states of the cluster may be controlled by the geometries of the hydrogen bonds.[770]

The cubane-like Fe_4S_4 cluster is also present in synthetic analogues of general formula $[Fe_4S_4(SR)_4]^{n-}$, where $n = 2$ or 3, and R may be an alkyl or aryl group. The singly charged cluster analogous to oxidized HiPIP has not been prepared. These clusters may be synthesized by facile 'self-assembly' reactions from $FeCl_3$, NaOMe, RSH and NaSH.[771,772] Clusters may also be extruded from iron-sulfur proteins (as may the other iron-sulfur clusters) by the use of 80% DMSO and benzenethiol, which cause the unfolding of the protein and the displacement of the native cysteine ligand from the iron. The extruded cluster will then contain the benzene thiolate as the terminal ligand, and may be compared with the synthetic analogue. This approach allows the identification of the number and type of the iron-sulfur clusters present in iron-sulfur proteins and in more complex enzymes such as nitrogenase. The success of this technique depends upon the resistance of the cluster to degradation during the extrusion process.

As indicated in equation (24), these clusters are mixed-valence compounds containing Fe^{II} and Fe^{III}. It was noted that the two-iron proteins involved localized valencies, with good evidence for Fe^{II} and Fe^{III} in the reduced protein. This does not appear to be case for the four-iron clusters, as shown particularly by the use of Mössbauer spectroscopy which has demonstrated the equivalence of all four iron centres in the cube. Thus for the C^{2-} state (where $C = [Fe_4S_4(SR)_4]$), in both model compounds and protein-bound clusters, there are four equivalent iron centres with average oxidation state +2.5. Inequivalence between the iron atoms could not be detected in the quadrupole splitting. The results for oxidized HiPIP from *Chromatium* show no more than slight inequivalence of the four iron atoms with an average oxidation state of +2.75. The Mössbauer evidence for reduced Fd from *Bacillus stearothermophilus* does show some differences between pairs of iron atoms, but the four atoms are nearly equivalent with average oxidation state +2.25. Thus, it appears that the Fe_4S_4 cluster is largely a valence-delocalized structure in all oxidation states. A molecular orbital model for the delocalized *d*-electron system of Fe_4S_4 clusters has been proposed.[773]

There have been many studies on the electronic properties of the synthetic and natural clusters. Work has also focused more recently on the preparation of soluble clusters which do not undergo hydrolysis, such as $[Fe_4S_4(SCH_2CH_2OH)_4]^{2-}$ and $[Fe_4S_4(S(CH_2)_nCO_2)_4]^{6-}$, and also on clusters in which the terminal ligands are oxygen donors (carboxylate[774] or phenoxide[775]) or halides.[758] The cluster $[Fe_4S_4(SPh)_4]^{2-}$ may be prepared in aqueous-based media.[759] There have also been some interesting studies in which synthetic clusters have been complexed with peptides to make small iron-sulfur proteins.[776,777] The cluster $[Fe_4S_4(SBu^t)_4]^{2-}$ has been reacted with several cysteine-containing peptides in order to investigate the effect on the cluster of the number and spacing of the cysteine residues and the nature of the non-cysteine side-chains.[778,779]

A major reason for carrying out these studies[776,777,780,781] has been an interest in the factors that control the redox potentials of the native iron-sulfur proteins that involve the C^{2-}/C^{3-} couple. A number of these have midpoint reduction potentials close to −400 mV, while others vary from −280 mV (*B. stearothermophilus* ferredoxin) to −490 mV (*Chromatium vinosum* ferredoxin, 2[4Fe-4S]). A synthetic cluster such as $[Fe_4S_4(SCH_2Ph)_4]^{n-}$ has a redox potential of −1250 mV (SCE) in DMF solution, compared to −930 mV (SCE) in DMSO for the protein from *Clostridium pasteurianum*. The presence of electron-attracting groups (and a solvent of higher dielectric constant) results in positive shifts in potential in the model clusters, while the redox potentials of $[Fe_4S_4(Ac\text{-}Cys\text{-}NHMe)_4]^{2-}$ and $[Fe_4S_4(t\text{-}Boc\text{-}(Gly\text{-}Cys\text{-}Gly)_n\,NH_2]^{2-}$ are fairly close to that of denatured *Cl. pasteurianum* ferredoxin in 80% DMSO-water.[776] The redox potentials of

iron-sulfur proteins are thought to be higher than those of Fe_4S_4 model clusterrs by 60–120 mV due to the extrinsic effects of the protein.

The detailed redox potentials of clusters cycling between C^{2-} and C^{3-} have also been attributed to the presence of the NH···S hydrogen bonding. This has been explored in a general sense by the synthesis of clusters having thiols with acidic hydrogens,[780] and more specifically by the study of redox potentials of synthetic [4Fe-4S]-peptide complexes which attempt to produce a similar hydrogen bonding situation. The latter work[781] involved the comparison of redox potentials of the two clusters $[Fe_4S_4(Z\text{-Cys-Gly-OMe})_4]^{2-}$ and $[Fe_4S_4(Z\text{-Cys-Gly-Ala-OMe})_4]^{2-}$, where Z= carbobenzoxy. The latter species contains the Cys-Gly-Ala sequence responsible for the formation of the intramolecular NH···S hydrogen bond in *Peptococcus aerogenes* ferredoxin, which occurs between the S atom of the Cys residue and the amide NH of the Ala residue. The former species will not be able to form this intramolecular hydrogen bond. The 4Fe model complex of Z-Cys-Gly-Ala-OMe shows a more positive potential (140 mV) than the model with Z-Cys-Gly-OMe in chloroform solution at 243 K. However, the difference is only supported in a solvent with low dielectric constant and at low temperature. It is suggested that the NH···S hydrogen bond produces a conformational folding of the tripeptide, which is stabilized by low temperature. This results in a hydrophobic environment. The conformational folding of the tripeptide was supported by CD and IR spectra.

The kinetics of oxidation and reduction of [4Fe-4S] proteins by transition metal complexes and by other electron-transfer proteins have been studied. These reactions do not correlate with their redox potentials.[782] The charge on the cluster is distributed on the surface of HiPIP through the hydrogen bond network, and so affects the electrostatic interaction between protein and redox agents such as ferricyanide, Co^{III} and Mn^{III} complexes.[782,783] In some cases, limiting kinetics were observed, showing the presence of association prior to electron transfer.[783]

The reaction between HiPIP and cytochrome *c* or bacterial cytochromes[784] involves specific sites on both proteins, although no kinetic evidence for association was found. Reaction between *Chr. vinosum* and *Rhodopseudomonas gelatinosa* HiPIPs with modified cytochrome *c* (trinitrophenyllysine-13)[785] was more rapid than for the unmodified cytochrome *c* since modification of Lys-13 destabilizes the heme crevice, and because the hydrophobic TNP group facilitates electron transfer by interacting with a hydrophobic region of the HiPIP.

The self-exchange rate constants for HiPIP are rather low, reflecting the buried nature of the Fe_4S_4 cluster.[783] Self-exchange rate constants for other tetranuclear clusters, including model compounds,[786] are in the range 10^6–10^7 $dm^3\ mol^{-1}\ s^{-1}$. It is suggested[787] that electron transfer to C^{2-} to give C^{3-} involves a change from a compressed tetragonal geometry to give an elongated geometry, and a structural reorganization energy of 5.9 kJ mol^{-1}.[788] Additional contributions to the activation energy for electron transfer in the iron-sulfur proteins will therefore represent constraints imposed by any structural reorganization in the proteins.

62.1.5.4.4 Three-iron proteins

In contrast to the well-defined situation described in the previous sections for the one-, two- and four-iron clusters in iron-sulfur proteins, there is still much uncertainty about the structural and biochemical aspects of the three-iron clusters.[739,741]

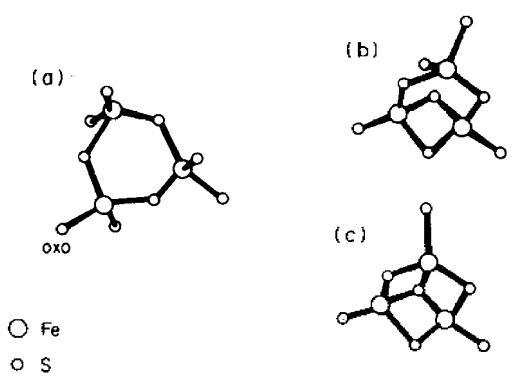


Figure 31 Possible structures for the three-iron proteins: (a), the the 3Fe-3S cluster in *Azotobacter vinelandii* FdI; (b) and (c), the 3Fe-4S cluster in *Desulfovibrio gigas* FdII

The first example of a three-iron cluster was found in the iron-sulfur protein designated ferredoxin I (FdI) from *Azotobacter vinelandii*, which was described as containing seven or eight iron atoms per molecule, and was thought to contain two [4Fe-4S] clusters, both of the HiPIP type but with midpoint redox potentials of +350 and −420 mV. Extrusion experiments gave conflicting conclusions. An X-ray diffraction structure at 4 Å resolution suggested that there was only one [4Fe-4S] cluster, and that the second was a two-iron cluster.[789] Refinement to 2.5 Å showed that the second structure was of a new structural type, namely a three-iron protein. This is shown in Figure 31, and is a [3Fe-3S] structure, approximately planar and with distorted tetrahedral coordination around each iron. The structure involves internal Fe—S—Fe angles of 126°, 131° and 113°, very much larger than those found in the [2Fe-2S] and [4Fe-4S] clusters, and hence Fe · · · Fe distances of about 4.1 Å compared to 2.7 Å in the other structural types. The structure also shows the absence of NH···S hydrogen bonds, discussed earlier for other clusters. The 3Fe site in *A. vinelandii* FdI is present as $[Fe_3S_3(S\text{-}Cys)_5(oxo)]$, with an unidentified ligand, possibly solvent water or hydroxyl.[790,791]

Prior to the X-ray crystallographic results, the use of Mössbauer and ESR spectroscopy had led to the proposal that a high-potential [4Fe-4S] cluster and a low-potential, novel three-iron centre were present in *A. vinelandii* FdI.[792]

Some 10 further examples of three-iron centres are now known. Some of them are derived from [4Fe-4S] clusters, and may be artifacts of the extraction procedure. This may be illustrated with reference to aconitase, an enzyme that catalyzes the stereospecific conversion of citrate to isocitrate *via cis*-aconitate in the tricarboxylic acid cycle. The enzyme is inactive after aerobic isolation, but may be activated by reduction and addition of Fe^{II}, or by long standing. It appears that the inactive form of the enzyme contains a three-iron cluster, formed by degradation of a [4Fe-4S] cluster during extraction. Activation involves the reformation of the [4Fe-4S] cluster, either by addition of Fe^{II} or by cannibalization of the three-iron cluster, which occurs on long standing.[793] Evidence for this reversible interconversion of 3Fe and 4Fe clusters has been found by the use of resonance Raman spectroscopy, which confirms that activation of aconitase is accompanied by a change in the characteristic Raman spectrum of the iron-sulfur cluster from that of a 3Fe cluster to that of a [4Fe-4S] cluster.[794] The iron-sulfur cluster from inactive aconitase has the stoichiometry of [3Fe-4S], while the molecular weight (83 000) and amino acid composition of the protein have been redetermined.[795,796]

The existence of the [3Fe-4S] cluster having a different stoichiometry from that reported for the *A. vinelandii* FdI ([3Fe-3S]) represents a difficulty that will be enlarged upon later in this section.

Conversion of four-iron clusters into three-iron clusters by treatment with ferricyanide has been demonstrated for ferredoxin from *Clostridium pasteurianum*[797] and from *Bacillus stearothermophilus*.[798] The reverse process, the conversion of a three-iron cluster into a [4Fe-4S] cluster, has been achieved by incubation with Fe^{2+} and S^{2-} in the presence of dithiothreitol for ferredoxin from *Desulfovibrio gigas*.[799] The reconstitution of [4Fe-4S] clusters allows the possibility of incorporating an isotopic label into the cluster.

A number of iron-sulfur proteins with seven iron atoms have now been isolated and provide useful parallels with *A. vinelandii* FdI. These include iron-sulfur proteins from *Thermus thermophilus*,[800,801] *Mycobacterium smegmatis*[801,802] and *Pseudomonas ovalis*.[801] These four seven-iron proteins have high sequence homology, and so it might be expected that they all should have the [3Fe-3S] cluster. However, they have been described as [4Fe-4S] and [3Fe-*n*S] proteins in Table 18 as their structures have not been determined, and there is some doubt over the [3Fe-3S] structure. The presence of the oxidized 3Fe protein is shown by a $g = 2.01$ ESR signal. In the case of *T. Thermophilus*, *M. smegmatis* and *Ps. ovalis* proteins, the [4Fe-4S] clusters have lower redox potentials than the 3Fe cluster, which is not the case for the FdI from *A. vinelandii*. This may reflect different patterns in hydrogen bonding but does seem strange.

A range of techniques, *i.e.* Mössbauer, magnetic circular dichroism, ESR and resonance Raman spectroscopy together with EXAFS results on two 3Fe proteins, have been applied to the problem of the structure of these three-iron clusters. These results have been comprehensively and critically reviewed.[741]

The 3Fe cluster in FdII from *D. gigas* has been particularly well studied, as it contains only one type of cluster and is usually free from adventitious iron. The use of Mössbauer spectroscopy shows that the oxidized cluster contains three equivalent iron centres, with an isomer shift appropriate for high-spin Fe^{III} in a tetrahedral environment of sulfur atoms.[803] Addition of one electron to give the reduced form of the cluster results in one iron centre remaining as Fe^{III} and the other two remaining equivalent and having an oxidation state of +2.5. Thus, the valencies

are delocalized over two iron atoms only. The key features of the Mössbauer spectrum of *D. gigas* FdII are also seen in aconitase, *B. stearothermophilus* and *M. barkeri* 3Fe proteins, and also, interestingly, in FdI from *A. vinelandii*. Mössbauer spectroscopy of the oxidized *D. gigas* FdII in the presence of a magnetic field shows the presence of three iron sites, each characterized by three hyperfine coupling constants.[803] This does not mean that there are structural differences between the three iron centres, as these same features are reproduced in a theoretical analysis of spin coupling in a cluster of three high-spin Fe^{III} centres.[804]

Resonance Raman spectroscopy has been of considerable use in characterizing 3Fe and 4Fe proteins.[794] Thus, bands have been assigned in [4Fe-4S] clusters to ν_{Fe-S} (335 cm^{-1}) and ν_{Fe-SR} (356 cm^{-1}) and in the 3Fe cluster of FdII (*D. gigas*) to ν_{Fe-S} (345 cm^{-1}) and ν_{Fe-SR} (365 cm^{-1}).[805]

EXAFS data are available on FdII from *D. gigas*[806] and aconitase,[807] for frozen, aqueous samples. Their structures are similar. In the case of FdII, two peaks were seen, giving bond lengths of 2.25 and 2.70 Å for Fe—S and Fe—Fe respectively. These values are quite unlike those found for *A. vinelandii* Fd (Fe—Fe = 4.1 Å). The EXAFS data for *D. gigas* FdII appear very similar to those observed for [4Fe-4S] clusters. It appears, therefore, that either the 3Fe cluster has a mobile structure or that one of the two proposed structures is substantially incorrect. The [3Fe-4S] structure from *D. gigas* and aconitase could be formed by removing an iron(II) ion from the corner of the [4Fe-4S] cube, with the generation of a free thiol chain (Figure 31b). The alternative structure (31c) maintains all four original cysteine groups as ligands in the [3Fe-4S] cluster. It possesses two types of iron coordination site, while the equivalent pair could correspond to the pair seen in the Mössbauer spectrum of the reduced 3Fe cluster which have an average oxidation state of +2.5.

It is important that model compounds for 3Fe clusters are synthesized in order to allow a full comparison of the properties of these various structures. The compound $(Et_4N)_2[Fe_3S_7C_{30}H_{36}]\cdot MeOH$ was prepared[808] by reacting 1,2-bis(mercaptomethyl)-4,5-dimethylbenzene and sodium methoxide with $FeCl_3$ and *p*-thiocresol in anhydrous methanol, followed by precipitation with Et_4NCl. The iron-sulfur cluster has the stoichiometry $Fe_3S(SRS)_3^{2-}$ with the iron atoms forming a triangle and the inorganic sulfide lying above the centre of the triangle. The coordination around each iron atom is completed by three mercapto sulfur atoms, giving a distorted tetrahedral array of sulfur atoms around each iron atom. Each bismercapto ligand has a unidentate and a bridging mercapto group. The structure in Figure 31b has similarities with this model compound, but the model does have three Fe^{II} centres in the cluster, unlike the [3Fe-4S] cluster.

The three-iron cluster $[Fe_3S(S_2\text{-}o\text{-xyl})_3]^{2-}$, where S_2-*o*-xyl = *o*-xylene-α,α-dithiolate, has a pyramidal $[Fe_3(\mu_3\text{-}S)]^{4+}$ central unit.[809]

Some linear structures are known, as in $(Et_4N)_3[Fe_3S_4(SR)_4]$, where R = Et or Ph.[752,810] The iron atoms are bridged by two sulfide ions and the terminal positions are filled by the thiol groups, to give a tetrahedral environment around each iron atom. The ESR spectra of these models do not correspond to the spectra of any known iron-sulfur protein, with the exception of unfolded aconitase, which thus appears to have a linear 3Fe core.[811] The model also represents isolated sections of the polymer $KFeS_2$.

The $[Fe_3S_4(SEt)_4]^{3-}$ undergoes conversion into the [4Fe-4S] cluster in acetonitrile with $FeCl_2$ alone or in the presence of NaSEt.[752] The molybdenum complex $[Mo_3S_4(SCH_2CH_2S)_3]^{2-}$ contains the $Mo_3S_4^{4+}$ core, and shows similarity in its resonance Raman spectrum with [3Fe-4S] proteins.[812]

It is still uncertain whether any of these three-iron clusters have any physiological role at all. It is evident that 3Fe and [4Fe-4S] clusters are interconverted readily, and a 3Fe cluster may lie on the biosynthetic route that leads to the formation of [4Fe-4S] clusters. There is some evidence that the 3Fe cluster of FdII can participate in electron transfer between redox proteins, but again this has no ultimate significance, as a variety of added mediator complexes are able to carry out such a function. It has been suggested recently that the 3Fe centre in aconitase is capable of promoting partial catalytic activity of the enzyme.[813]

62.1.5.4.5 Characterization of iron–sulfur clusters

Some of the earlier approaches to the characterization of iron-sulfur clusters have proved to be inadequate in the presence of mixtures of clusters and, particularly, three-iron clusters. Thus the technique of core extrusion has worked well for [2Fe-2S] and [4Fe-4S] cores, but led to confusing results for aconitase and FdI from *A. vinelandii* as [2Fe-2S] cores were extruded.

Indeed it may be that 3Fe clusters are always extruded as [2Fe-2S] clusters, an observation that would have structural implications. The use of resonance Raman and MCD spectroscopy[814] has allowed valuable distinctions to be made between these clusters, while ESR techniques seem to be of particular value. Thus, the first indication of a 3Fe cluster in an iron-sulfur protein has usually been the observation of a $g = 2.01$ signal in the ESR spectrum, but it should be noted that there may be confusion with oxidized HiPIP clusters.

ESR-active clusters will be oxidized 3Fe, oxidized HiPIP, reduced 2Fe and reduced 4Fe (Fd). Further distinction may be made by consideration of the dependence on magnetic fields of the shift in g value induced by an externally applied electric field (linear electric field effect). This effect is similar for 3Fe and 4Fe ferredoxins, but is considerably different for both 2Fe and HiPIP clusters, which also differ from each other. Thus, all four classes of iron-sulfur protein (2Fe, 3Fe, Fd and HiPIP) may be distinguished by a combination of ESR and LEFE properties.[814a]

The study of such magnetic field dependence of the LEFE in ESR spectroscopy has allowed the demonstration that the iron-sulfur cluster in beef heart succinate-ubiquinone oxidoreductase is a 3Fe cluster.[815]

62.1.5.4.6 Enzymes having iron–sulfur clusters

The iron-sulfur cluster is often present as the prosthetic group in oxidoreductases where the couple of the substrate is below 0 mV. This reflects the reducing power of the iron-sulfur cluster. There are, however, a small number of iron-sulfur-containing enzymes that function in the positive redox range. These are often associated with bacterial nitrate and nitrite metabolism. The least complicated enzymes contain no additional cofactor, while others contain a number of additional cofactors.

Iron-sulfur enzymes include hydrogenase, 4-methoxybenzoate-*O*-demethylase and those bound to photosynthetic membranes. Iron-sulfur enzymes that contain thiamine pyrophosphate are involved in the reduction of ferredoxin by pyruvate. A number of dehydrogenases are iron-sulfur-flavin enzymes, including succinate dehydrogenase, NADH dehydrogenase, formate dehydrogenase and dihydroorotate dehydrogenase, together with glutamate synthase and trimethylamine dehydrogenase. Iron-sulfur heme enzymes are typified by dissimilatory sulfite reductase, while iron-sulfur-molybdenum groups are involved in nitrogenase, nitrate reductase (dissimilatory) and CO_2 reductase.

62.1.5.5 Binuclear, Oxo-bridged Iron Centres and the Iron-tyrosinate Proteins

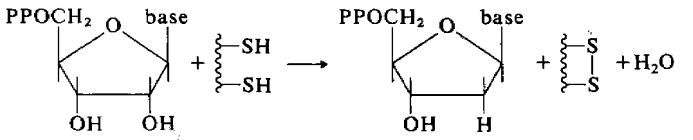
The emphasis on the study of hemoproteins and the iron-sulfur proteins often distracts attention from other iron proteins where the iron is bound directly by the protein. A number of these proteins involve dimeric iron centres in which there is a bridging oxo group. These are found in hemerythrin (Section 62.1.12.3.7), the ribonucleotide reductases, uteroferrin and purple acid phosphatase. Another feature is the existence of a number of proteins in which the iron is bound by tyrosine ligands, such as the catechol dioxygenases (Section 62.1.12.10.1), uteroferrin and purple acid phosphatase, while a tyrosine radical is involved in ribonucleotide reductase. The catecholate siderophores also involve phenolic ligands (Section 62.1.11). Other relevant examples are transferrin and ferritin (Section 62.1.11). These iron proteins also often involve carboxylate and phosphate ligands. These proteins will be discussed in this section except for those relevant to other sections, as noted above.

The X-ray absorption spectra of a series of 28 model Fe^{III} complexes and those of ovatransferrin, protocatechuate 3,4-dioxygenase and catechol 1,2-dioxygenase have been analyzed, and appear to give information on the coordination number of the protein-bound iron. Thus the transferrin complexes appear to be six- or seven-coordinate, while the dioxygenase complexes could be five- or six-coordinate.[816]

62.1.5.5.1 Ribonucleotide reductase

Reduction of ribonucleotides to deoxyribonucleotides, the essential first step in the synthesis of DNA, is catalyzed by the enzyme ribonucleotide reductase (equation 25). Three different types of ribonucleotide reductase are known, which differ in their requirement for metal, namely cobalt

as adenosylcobalamin, protein-bound iron and, less usually, protein-bound manganese. The cobalt-containing enzyme is discussed in Section 62.1.6. The ribonucleotide reductases have been reviewed comprehensively.[817-819]



(25)

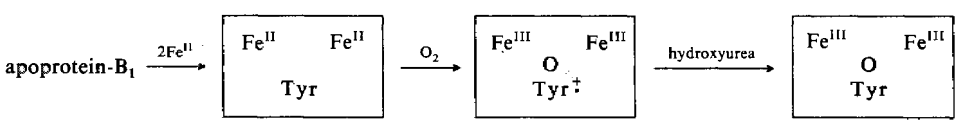
The iron protein has been found in animals, viruses and some prokaryotic organisms. The best studied example is from *Escherichia coli*.[819] The enzyme consists of two subunits, B_1 and B_2. Subunit B_1 has a molecular weight of 160 000 and is made up of two polypeptide chains. It contains redox-active SH groups, which play a role in the reaction, and has two binding sites for substrates and sites for effector molecules. It can bind any of the four ribonucleotide substrates. Subunit B_2 has a molecular weight of 78 000 and also has two polypeptide chains. It contains a dimeric oxo-bridged iron site associated with a remarkably stable tyrosine radical. The formation of the active enzyme from B_1 and B_2 requires the presence of magnesium ions.

The dimeric iron centre has a number of similarities to the dimeric iron centre in the oxygen carrier hemerythrin. While the two proteins are functionally unrelated, ribonucleotide reductase does require oxygen. Evidence from Mössbauer and Raman spectroscopy and from magnetic measurements shows that subunit B_2 contains two non-equivalent high-spin Fe^{III} centres antiferromagnetically coupled by a μ-oxo bridge, probably with an FeOFe angle of about 130°. The tyrosine radical is manifested in an ESR signal consisting of a doublet at around $g = 2.0047$. The identification of the radical as a tyrosine group resulted from elegant isotopic substitution experiments.[820]

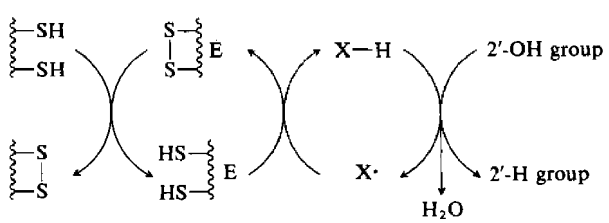
The radical is formed by the loss of an electron from the aromatic ring to give an oxidized tyrosine species, in which the unpaired electron is delocalized over the phenyl ring. The radical species survives almost indefinitely when the protein is stored at −70 °C. This stability is suggested to result from the location of the tyrosine group in a pocket in the protein. The radical is not formed in the apoprotein.

The radical is destroyed by hydroxyurea and hydroxylamine, which accounts for the ability of the former compound to inhibit the synthesis of the DNA. Subtraction of the UV-vis spectrum of the hydroxyurea-treated protein B_2 from that of the native protein thus gives the spectrum of the tyrosine radical, which shows considerable similarities with the known spectrum of the 2,4,6-tri(2-methylpropane)phenoxy radical.

Apo-B_2 takes up Fe^{II} from the medium, and the tyrosine radical is generated spontaneously if dioxygen is present. The dioxygen may be reduced to give the oxo bridging group, with concomitant oxidation of two Fe^{II} and tyrosine. These redox reactions are represented in equation (26).



(26)



(27)

E = enzyme
X—H = tyrosine

The reduction of the 2'-hydroxyl group in the ribose ring is coupled to the cysteine-to-cystine oxidation occurring in the B_1 subunit. This process cannot occur directly and other intermediates are necessary, with NADPH as the final reductant. Reduced thioredoxin (or glutaredoxin) transfers electrons to an enzyme disulfide bridge, which in turn reduces the tyrosine radical which then interacts with the 2'-OH group. Little is known about the way in which the 2'-OH group is activated

for reduction (equation 27). The role of the dimeric iron centre appears to be linked to the formation and stabilization of the tyrosine radical.

62.1.5.5.2 Purple acid phosphatase

A number of purple acid phosphatases[821] have been isolated from animal sources, including bovine spleen, rat bone and the enamel organ of rat molars. Other phosphatases may belong to this class but the identification is not yet certain. Purple acid phosphatase from the sweet potato, as noted in Section 62.1.3.6.1, contains manganese.

In addition, a glycoprotein found in porcine uterine flushings contains iron and possesses acid phosphatase activity. This protein has been called uteroferrin, in view of its proposed role in the transport of iron from maternal to foetal circulation. On reduction, uteroferrin becomes pink in colour.

The bovine spleen enzyme is dimeric, has a molecular weight of nearly 40 000 and contains two iron centres.[822] One of these can be removed reversibly by treatment of the protein with dithionite.[823] Conflicting results have been reported for uteroferrin; one group has found two iron atoms per 40 000 molecular weight,[824] while another group reported one iron atom and molecular weight 35 000.[825]

Little is known about the mechanism of action of the purple acid phosphatase. The beef spleen enzyme as isolated contains one tightly bound phosphate,[821] but it is not certain whether this corresponds to a phosphorylated amino acid residue as found for other phosphatases. Addition of phosphate causes a shift in the visible spectrum of the enzyme.

The two iron atoms in acid phosphatase appear to have different reactivity to chelating agents. One iron, as noted earlier, may be removed by treatment with dithionite. This may be replaced by Zn^{2+}, and the resulting mixed-metal enzyme shows only half the absorption at 550 nm of the native two-iron form. it also fails to undergo the purple-to-pink colour changes.

Resonance Raman spectra of one-iron preparations of uteroferrin and the splenic acid phosphatase show that tyrosine is a ligand.[826] The intense visible spectra of these proteins is due to tyrosine → Fe^{III} charge-transfer transitions. Two or three tyrosine residues are implicated.

ESR spectroscopy of one-iron uteroferrin shows the presence of a novel rhombic $g = 1.74$ signal, indicating a fundamental difference from the iron-binding site in transferrin, which also contains Fe^{III}-tyrosinate groups. Magnetic measurements on purple and pink (reduced) forms of the splenic acid phosphatase show in both cases that the two iron centres are antiferromagnetically coupled with $S = 0$ and $S = \frac{1}{2}$ ground states respectively. It appears that the pink protein has Fe^{III}- and Fe^{II}-coupled centres, while the purple protein has two high-spin Fe^{III} centres. The purple-to-pink colour change is associated with a one-electron reduction of the binuclear iron centre. This may mean that one of the iron atoms is coordinated to both tyrosine ligands, and that this is the iron centre that remains Fe^{III}. The second reducible iron centre will not have tyrosine ligands.

It has been shown[826a] that the analysis of iron in uteroferrin is dependent on the presence of phosphate. Analysis of the native enzyme with one tightly bound phosphate gives an incorrect low answer suggesting the presence of only one iron.

62.1.5.5.3 Other binuclear oxo-bridged iron centres

It seems probable that other redox centres contain this binuclear iron structure, but that this has not yet been recognized. For example, a non-heme iron protein of the methane monooxygenase from *Methylococcus capsulatus* (Bath), which functions as the oxygenase in equation (28), has been described as having a novel iron centre which is not an iron–sulfur cluster.[827] This may well be an oxo-bridged system. Analysis suggests 2.3 Fe per molecule of protein.

$$CH_4 + O_2 + NADPH + H^+ \rightarrow CH_3OH + NADP^+ + H_2O \qquad (28)$$

Phenylalanine hydroxylase from rat liver contains a tightly bound non-heme iron that is essential for the activity of the enzyme. The enzyme functions aerobically to produce tyrosine from phenylalanine and a tetrahydropterin.[828]

62.1.6 THE BIOCHEMISTRY OF COBALT

Naturally occurring cobalt compounds involve the corrin ring system shown in Figure 2. This group provides four in-plane nitrogen donor atoms. In addition, one axial position is filled by the N(3) atom of a 5,6-dimethylbenzimidazole ring, which is linked to the corrin group *via* a phosphodiester group. This five-coordinate complex is a cobalamin. Vitamin B_{12} contains cyanide in the second axial position, but this is an artifact of the isolation procedure and has no biological significance. Vitamin B_{12} is thus named cyanocobalamin. Figure 32 shows the structure of coenzyme B_{12}, adenosylcobalamin, in which the axial position is filled by the 5′-C of 5′-deoxyadenosine. The presence of this organocobalt compound of remarkable stability has attracted much attention, and a range of very stable organocobalt compounds have subsequently been synthesized in model studies for B_{12}. Adenosylcobalamin is an essential coenzyme for at least a dozen enzymes. It is agreed that Co—C bond breaking and formation is a key step in these processes. Methylcobalamin is a second coenzyme with a Co—C bond, and contains a methyl group in the upper axial position. The ability of methylcobalamin to transfer a methyl group to other metals has led to the formation of methyl derivatives of the metal. Such reactions are significant in environmental considerations. These cobalamins are Co^{III} low-spin compounds, with charge neutralization resulting from the phosphodiester group, the corrin ring and the organo axial ligand.

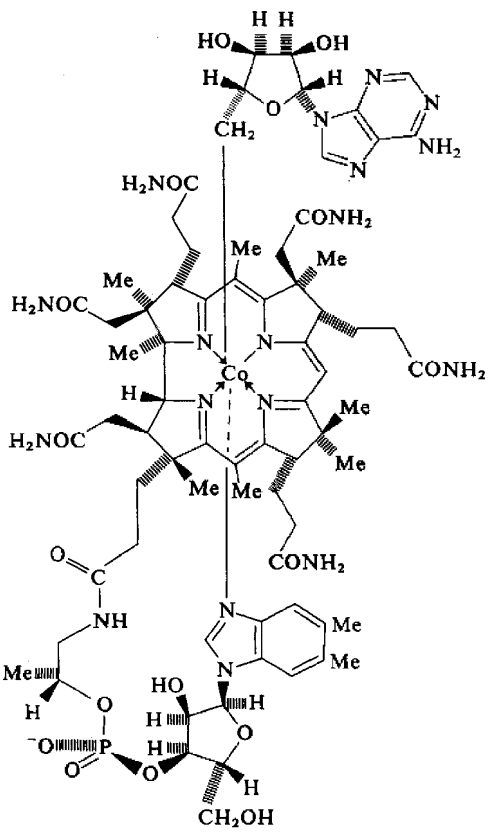


Figure 32 The structure of adenosylcobalamin

The benzimidazole axial ligand is displaced on hydrolysis to give the cobinamides.

Very many reviews and books[829–832] are available on the B_{12} coenzymes. Reviews have usually focused on particular areas including Co—C bond formation and cleavage[833] and model compounds[834–837] (having an inorganic emphasis), environmental chemistry[838] and biochemical aspects.[839–846]

62.1.6.1 Some General Considerations on B_{12} Coenzymes and Model Compounds

Naturally occurring cobalamins contain low-spin cobalt (III), but they undergo sequential one-electron reductions to give the cobalt(II) and cobalt(I) forms, known as B_{12r} and B_{12s}. Aqua

and hydroxo cobalamins are known as B_{12a} and B_{12b} respectively. The B_{12s} aquacob(I)alamin is a powerful nucleophile and is rapidly oxidized by dioxygen and water at pH below 8. It will react with a range of alkylating agents to reform the alkylcob(III)alamin (equation 29). The Co—C bond may also be formed from Co^{II} or Co^{III} species (equations 30 and 31).

$$Co^{I} + R^{+} \rightarrow CoR \quad (29)$$

$$Co^{II} + R\cdot \rightarrow CoR \quad (30)$$

$$Co^{III} + R^{-} \rightarrow CoR \quad (31)$$

A great deal of work has been carried out using model compounds. Of particular note are the bis(dimethylglyoximato)cobalt complexes, known as the cobaloximes. These compounds are square planar, and readily add on axial ligands or form stable organic derivatives. They will also substitute for cobalamins in certain reactions. Their similarity to the cobalamins probably reflects the presence of four strong, in-planar donor atoms. It is not surprising that Schiff base complexes of cobalt also serve as good models,[847,848] as do a range of tetranitrogen macrocycles such as porphyrins and phthalocyanines. However, models have been reported which involve a terdentate meridionally orientated ligand, and either a bidentate diamine or two monodentate ligands, plus an alkyl group.[849] These models lose alkyl groups readily.

As will be noted later, it is commonly thought that homolytic cleavage of the Co—C bond is an important initial stage in the reactions of cobalamins. Accordingly, there has been much interest in the formation of Co—C bonds, the factors that determine their stability, and the cleavage of these Co—C bonds.

62.1.6.1.1 Organocobalt compounds: formation and cleavage of the Co—C bond

Organocobalt compounds may be prepared by several routes.[833] The Co^{I} species is a useful starting point. This may be obtained by reduction of Co^{II} or Co^{III} compounds using hydrazine, thiols, chromium(II), borohydride and other reagents. The Co^{I} species will give a Co^{III} hydride species by reacting with a proton. Both the Co^{I} and the hydridocobalt(III) species are alkylated readily.

Cobalt(II) compounds react with an alkyl halide to give an organocobalt(III) compound, as shown in equation (32), where Y is an axial ligand. It takes place by three separate mechanisms, depending on the nature of the Co^{II} compound and the alkyl halide. The best known pathway involves the atom-transfer reactions shown in equations (33) and (34). The second mechanism involves electron transfer from the Co^{II} compound to the alkyl halide, which decomposes to give halide and organic radicals, which react with the Co^{II} compound. The third mechanism has been observed for the alkylation of vitamin B_{12r} by alkyl iodides.

$$2L_4YCo^{II} + RX \rightarrow L_4YCo^{III}R + L_4YCo^{III}X \quad (32)$$

$$L_5Co^{II} + RX \xrightarrow{\text{slow}} L_5Co^{III}X + R\cdot \quad (33)$$

$$L_5Co^{II} + R\cdot \rightarrow L_5Co^{III}R \quad (34)$$

Cobalt(II) compounds also undergo transalkylation reactions with organocobalt(III) compounds, probably *via* a transition state in which the two cobalt centres are bridged by the alkyl group.

Finally, Co^{III} compounds may react with carbanions to give organo derivatives, for example in the reaction of a Grignard reagent or an organolithium compound with a halogenocobalt(III) species.

The thermal decomposition of organocobalt Schiff base compounds py(saloph)CoR, with pyridine and R = alkyl or benzyl axial ligands, and saloph = *N*,*N*′-bis(salicylidene-*o*-phenylenediamine), proceeds at temperatures less than 100 °C in pyridine solution in the presence of a radical trap, *via* homolysis of the Co—C bond and the formation of Co^{III} compounds. Dissociation energies for the Co—C bonds have been determined[847,848] by kinetic and thermodynamic methods. Typical values are *D*(Co—Pr), 105; *D*(Co—Pr^{i}), 84; *D*(Co—Bu^{i}), 75; and *D*(Co—CH_2Ph), 92 kJ mol^{-1}. The Co—C bonds are weak, and show the effect of steric factors. There are many studies of this type.[850,851] In addition, the nature of the axial ligand is important. As the basicity of this ligand increases so does the strength of the Co—C bond. This may be understood, as the stronger base will favour the higher oxidation state and so disfavour Co—C bond homolysis.

The suggestion that Co—C bond dissociation energies lie in the range 84–125 kJ mol^{-1} is appropriate for the known rates of enzymatic reactions involving such dissociations. It is clear, too, from these model studies, that electronic and steric effects produced in the coenzyme by changes in the interactions in the coenzyme-enzyme complex could be significant in enhancing Co—C bond homolysis.

The alkyl ligand exerts a strong *trans* effect on the other axial ligand. The Co—benzimidazole bond length in cobalamin derivatives varies from 2.02 to 2.24 Å as the *trans* ligand is changed from cyanide to 5′-deoxyadenosyl.[852] The exchange of the ligand *trans* to the alkyl group in organocobalt(III) model compounds occurs by a dissociative mechanism. The rate of dissociation of benzimidazole from methylcobalamin has been estimated to be 2×10^3 s^{-1} by NMR techniques[853] and slightly higher by temperature jump studies.[854]

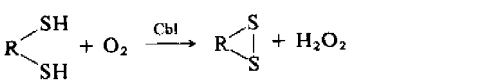
The cleavage of the Co—C bond in organocobalt compounds may occur by the reverse of the three pathways shown in equations (29)–(31). Bond homolysis has been particularly intensively studied, and may occur by photolysis or by thermolysis. Photolysis of the Co—C bond in methylcobalamin is accelerated by the presence of dioxygen, to give B_{12a} and formaldehyde. The slower rate of the anaerobic photolysis is suggested to result from recombination of B_{12r} and methyl radicals. The photolysis of adenosylcobalamin gives 5′-deoxy-5′,8-cycloadenosine and adenosine-5′-carboxaldehyde in the presence of O_2, and the cyclized product only in the absence of O_2.

Heterolytic cleavage of the Co—C bond can occur from the attack of electrophiles, including metals. The environmental methylation of Hg^{II} by methylcobalamin in a methanogenic bacterium[838] is a well-known example. In this case, the carbanion is transferred to Hg^{II} leaving the aquacob(III)alamin. A similar carbanion pathway holds for the methylation by methylcobalamin of lead(IV), thallium(III), palladium(II) and selenium. Dealkylations by Co^{II}, Cr^{II} and Sn^{II} involve radical reactions.

Heterolytic cleavage of the Co—C bond also occurs in reactions with acid, reducing agents, oxidizing agents and with nucleophiles such as alkali and cyanide. These topics have been comprehensively reviewed.[833]

62.1.6.1.2 Some reactions of cobalamins and cobinamides

Some representative reactions of these corrinoids are reviewed in this section. A great deal of evidence suggests that the interactions of cobalamins with sulfhydryl groups may be of biological significance. A number of cobalamin-dependent enzymes, including ribonucleotide reductase, either have thiol-containing subunits which are essential for activity, or interact with dithiol substrates. Again, the apoenzymes of diol dehydrase and methylmalonyl-CoA mutase are sensitive to reagents for SH groups, whereas the enzymes that contain adenosylcobalamin are protected from inactivation. Accordingly the reactions of cobalamins with thiols have been studied. Adenosylcobalamin and methylocobalamin and their cobinamide analogues catalyze the aerobic oxidation of 2-mercaptoethanol and dithioerythritol in a dark reaction.[855] In the latter case, the products were hydrogen peroxide and the cyclic disulfide of dithioerythritol, as shown in equation (35). The cobinamides were the most active catalysts, reflecting the availability of axial sites for the coordination of the thiol. The lower, but measurable, activity of the adenosyl- and methylcobalamins may be explained by the fact that the axial benzimidazole ligand equilibrates between 'base-on' and 'base-off' arrangements. The decrease in catalytic efficiency of the alkylcobalamin compared to the analogous alkylcobinamide correlates reasonably well with the ratio of base-on to base-off species for R—Cbl. It is suggested that the mechanism involves coordination of the thiol, followed by nucleophilic attack from a second thiolate anion to form a reduced cobalt(I) corrinoid and the disulfide. The reduced corrinoid is then oxidized by molecular oxygen to regenerate the active species. While of no direct biological significance, such studies confirm the existence of quite facile reactions between B_{12} coenzymes and thiol groups, including the possibility of coordination of substrate thiols to cobalt in enzymatic reactions.



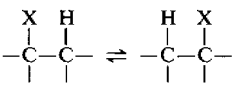
(35)

Cob(I)alamin reduces nitrate to ammonium ion at pH 1.5–2.5, with the initial step being rate determining.[856] Dioxygen adducts of vitamin B_{12r} are formed readily. EPR studies indicate that

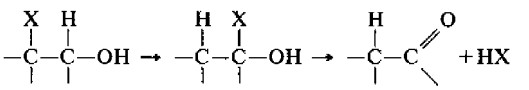
in the adduct the total spin density on the dioxygen is 0.7 ± 0.1, fairly close to a superoxide group and cobalt(III).[857] Again it is not certain if there is any biological significance to this work.

62.1.6.2 Adenosylcobalamin as a Coenzyme

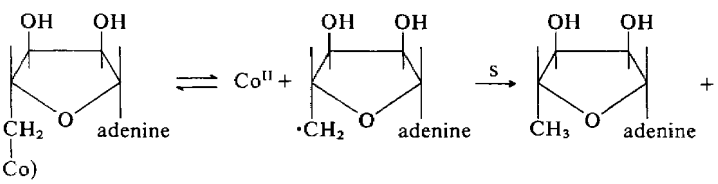
Adenosylcobalamin in association with an appropriate apoenzyme can catalyze a range of rearrangement reactions, typified by those given in equations (36) and (37), which usually involve a 1,2 hydrogen shift while a group X migrates in the opposite direction. Thus, in equation (36), a hydrogen atom and a group X interchange positions in a reversible reaction. The same process is involved in equation (37), but the group X is lost in a subsequent reaction so that the reaction is no longer reversible. Reactions of the reversible type where the group X involves C groups (*e.g.* alkyl or acyl) are described as Class A, and those with migrating N groups are Class B. The irreversible reactions are termed Class C. A number of these reactions are given in Table 19, which also includes the deoxyadenosylcobalamin-dependent ribonucleoside triphosphate reductase which is discussed in Section 62.1.6.2.1.



(36)



(37)



(38)

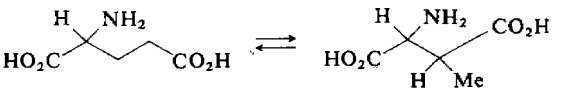
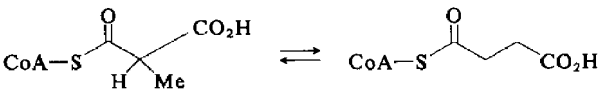
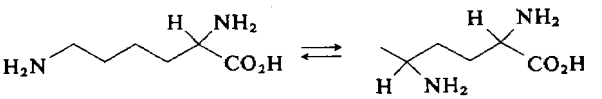
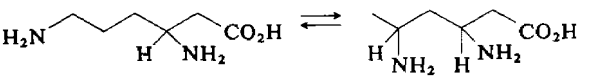
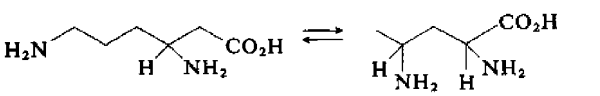
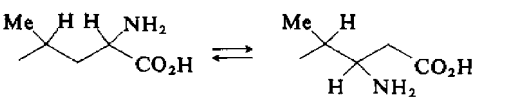
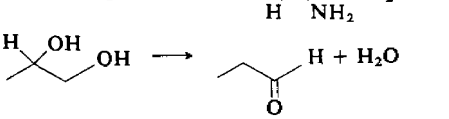
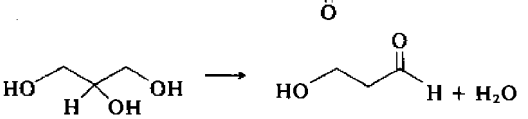
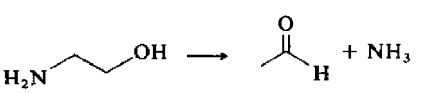
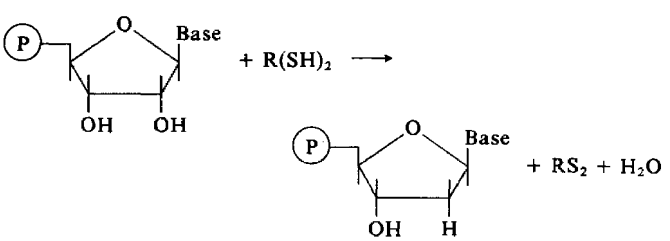
As emphasized earlier, it is fairly commonly accepted that the Co—C bond of adenosylcobalamin undergoes homolytic cleavage in these reactions. The adenosyl radical thus produced will then abstract a hydrogen atom from the substrate (equation 38). The formation of organic radicals and B_{12r} has been detected[841] on interaction of the coenzyme with certain of the apoenzymes from the enzymes listed in Table 19, particularly in the presence of substrate. Furthermore, tracer experiments show that the H atoms at position 5'-C in the deoxyadenosine exchange with substrate H atoms. A number of reactions could occur after the formation of the substrate radical. The substrate radical could undergo rearrangement to give a new radical, P·, which then reabstracts a hydrogen atom from the methyl group of the deoxyadenosine, regenerating the adenosyl radical.[858]

An alternative to the homolysis of the Co—C bond suggested above involves heterolytic cleavage to give cob(I)alamin and 4',5'-anhydroadenosine.[859] The cob(I)alamin then reacts with substrate to give an intermediate organocobalamin, which decomposes by an intramolecular 1,2 hydride shift to give cob(I)alamin and a product molecule. However, the weight of ESR evidence seems to confirm the important role of radicals. The appearance of the ESR spectrum occurs at a rate which is faster than, or comparable, to the turnover rate of the enzyme. Furthermore, in the reaction between ethanolamine ammonia lyase and ethanolamine, it appears[860] that during the steady state of the reaction, the cobalamin existed as 58% cob(II)alamin and 42% of a cob(III)alamin (which may be an organocobalamin derived from the substrate), while no evidence was found for a cob(I)alamin.

It appears, therefore, that emphasis should be placed on reactions involving Co—C bond homolysis. There does seem to be some evidence for binding of the substrate radical to the cobalt. The S· → P· rearrangement could take place on the cobalt. In addition, the cobalt centre could participate in redox reactions with the radical, to give oxidized S^+ or reduced S^- with production of Cbl^{I} and Cbl^{III} respectively. Species S^+ and S^- could reaarange to P^+ and P^-, which reform P· by reaction with Cbl^{I} and Cbl^{III} respectively. Model studies relevant to these pathways have been published.[861]

The roles of axial ligand and the protein in controlling Co—C bond homolysis have been explored. The benzimidazole group exists in 'on' and 'off' configurations. Model studies show

Table 19 Adenosylcobalamin-dependent Enzymes

Enzyme	*Class*	*Reaction catalyzed*
Glutamate mutase	A	
Methylmalonyl-CoA mutase	A	
α-Methyleneglutarate mutase	A	
α-Lysine mutase	B	
β-Lysine mutase	B	
D-Ornithine mutase	B	
L-Leucine-2,3-aminomutase	B	
Diol dehydrase	C	
Glycerol dehydrase	C	
Ethanolamine ammonia lyase	C	
Ribonucleotide reductase		

that facile Co—C homolysis seems to require only weakly donating ligands *trans* to the organo group. As noted earlier, strongly donating ligands will stabilize Co^{III} and so hinder cleavage. Accordingly, it has been suggested that a six-coordinate complex with a weak axial ligand most readily undergoes homolysis as the cobalt is kept in the plane of the corrin, and is hence more susceptible to steric effects, without undue stabilization of the Co^{III} state.[862]

The use of sterically hindered alkyl groups results in considerable distortion of the coordination sphere and enhanced tendency to homolysis. It is possible that binding of substrate induces a change in protein conformation, which will in turn introduce such steric strain around the cobalt. The advantage of this proposal is that the adenosyl radical would only be produced in the presence of substrate.

Metal-free corrinoids are produced by photosynthetic bacteria.[863] This allows the synthesis of analogues of vitamin B_{12} having other metals present, such as zinc, copper or rhodium. The

binding of these various metal-substituted vitamin B_{12} species to B_{12}-binding proteins has been studied. Analogues with a strong coordinative link between the heterocyclic base and the metal bind to a similar extent, but analogues where such a link is not possible (for example dicyanorhodibalamin) show markedly reduced binding. Thus, optimal recognition by vitamin B_{12} binding protein of B_{12} species seems to require the axial link with the base.

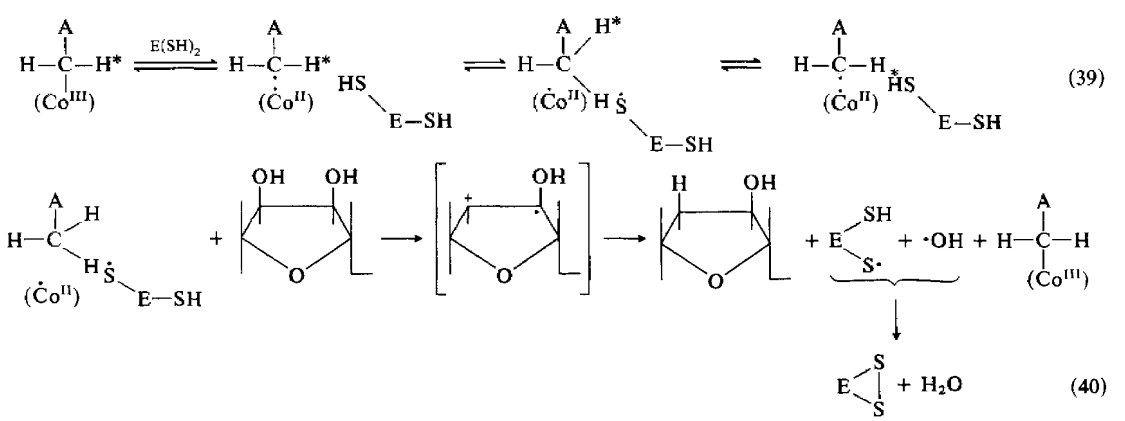
62.1.6.2.1 Ribonucleotide reductase

The iron-containing ribonucleotide reductases were considered in Section 62.1.5.5.1. The presence of a cobalt-requiring enzyme was demonstrated by the nutritional requirements of lactobacilli for B_{12} during DNA synthesis. Such organisms have very low levels or iron, and so use an alternative ribonucleotide reductase.[817] B_{12}-dependent ribonucleotide reductases are fairly common in microorganisms, *e.g. Clostridium sticklandii*, *Lactobacillus* spp., *Bacillus megaterium*, *Propionibacterium shermanii*, *Corynebacterium nephridii*, *Streptomyces aureofaciens*, *Paracoccus denitrificans*, *Pseudomonas* spp., *Thermus aquaticus*, *Rhizobium* spp., and for some blue-green algae (cyanobacteria).

Lactobacillus leichmanii ribonucleotide reductase has a molecular weight of 76 000, with a single polypeptide chain of about 690 amino acids. The large size of the apoenzyme probably reflects the need for it to have sites to interact with the coenzyme, a dithiol, a substrate and allosteric effectors. A transient radical species was observed during catalysis.

Rather similar ribonucleotide reductases have been isolated from the thermophile, *Thermus aquaticus* (MW = 80 000) and *Anabaena* (a blue-green alga) (MW = 72 000). The latter enzyme has an absolute requirement for divalent metal cations. The diphosphate reductase from *Corynebacterium* has a molecular weight of 200 000 and is made up of two subunits. Other enzymes appear to have tetrameric structures.[817]

It is noteworthy that the iron-containing ribonucleotide reductases contain a stable tyrosine radical. There is a parallel with the B_{12}-dependent ribonucleotide reductases where transient Co^{II} and R· species are formed. A dithiol is required to contribute two H atoms, which are ultimately transferred to the ribose 2'-OH group. In the presence of enzyme, the dithiol and a deoxyribonucleotide effector tritium from ^3H_2O exchanges with the cobalt-bound 5'-methylene group of the coenzyme. The use of rapid reaction techniques shows a rapid change in the UV-vis spectrum of the coenzyme due to the formation of a cobalt(II) species and the disappearance of this species after addition of substrate, with $t_{1/2} = 145$ ms.[865] ESR studies, using a freeze-quench method to cool samples to 80 K within milliseconds, established the formation and decay of a paramagnetic species,[866] formed at a maximum concentration level of about 60% of the coenzyme concentration. A possible scheme for these various hydrogen-transfer reactions is given in equations (39) and (40). Equation (39) shows how ^3H may exchange with the enzyme thiol group and hence into solvent water, while the reduction of the ribonucleotide substrate is shown in equation (40) and occurs *via* a hypothetical nucleotide radical[867,868] which abstracts H to regenerate the adenosyl radical.



62.1.6.3 Methylcobalamin as a Cofactor

This cofactor is involved in the synthesis of acetic acid from CO_2,[869] methionine from homocysteine (catalyzed by *N*-methyltetrahydrofolate-homocysteine methyl transferase)[870] and in the

synthesis of methane from CO_2 by the methane-generating bacteria (the methanogens). Methanogens obtain energy by the oxidation of dihydrogen under anaerobic conditions using carbon dioxide as the electron acceptor. A number of cofactors are involved in the sequence of reactions that leads to the formation of methane. These are one-carbon carriers, some of which have not yet been identified. Identified one-carbon carriers in methanogens include methylcobalamin[871] and coenzyme M.[872] The final step in methane production from CO_2 and H_2 involves CoM, because the purified methyl reductase in methanogens is specific for methyl CoM and not methylcobalamin. It appears that methylcobalamin reacts with coenzyme M, 2-mercaptoethanesulfonic acid, to give methylcoenzyme M in a reaction catalyzed by a methyltransferase enzyme. Finally, the methyl CoM is reduced to give methane (equations 41 and 42). It is noteworthy that methylcobalamin once more reacts with a thiol. The methyl coenzyme M reductase which catalyzes reaction (42) has a nickel-containing prosthetic group, factor F430, which is discussed in Section 62.1.7.2.

$$Me{-}B_{12} + HSCH_2CH_2SO_3^- \rightarrow B_{12r} + MeSCH_2CH_2SO_3^- \quad (41)$$

$$MeSCH_2CH_2SO_3^- \xrightarrow{H_2} CH_4 + HSCH_2CH_2SO_3^- \quad (42)$$

62.1.7 THE BIOCHEMISTRY OF NICKEL

Nickel is now firmly established[873] as an essential nutritional requirement for many eukaryotic and prokaryotic organisms. It is particularly well known as a component of the enzyme urease in plant cells growing on urea as a nitrogen source. This is a famous enzyme, as it was the first enzyme protein to be recrystallized, and for many years it represented the only example of a biological function for nickel. However, nickel is now recognized to be involved in a number of microbiological processes involving gases, such as the carbon monoxide dehydrogenases in acetogenic bacteria (equation 43), the methyl cofactor M reductase in methanogenic bacteria (equation 42); and in hydrogenases from several different types of bacteria (equation 44), including those which carry out the Knallgas reaction (equation 45). It seems appropriate that nickel should be involved in the catalysis of these reactions in view of the important role of nickel and nickel complexes in the catalysis of inorganic reactions of CO and of H_2.

$$CO + H_2O \rightarrow CO_2 + H_2;\ 2CO_2 + 4H_2 \rightarrow MeCO_2H + 2H_2O \quad (43)$$

$$H_2 + 2Ni^{III} \rightarrow 2H^+ + 2Ni^{II} \quad (44)$$

$$2H_2 + O_2 \rightarrow 2H_2O \quad (45)$$

As implied in equation (44), a feature of some of the microbial reactions is the apparent and, at first sight, surprising involvement of Ni^{III}. It should be noted that examples of Ni^{III} complexes are well known,[874] and usually involve macrocyclic ligands with nitrogen donors, or peptide ligands which in general provide deprotonated peptide groups as donor sites. These complexes are usually prepared by electrochemical oxidations.

62.1.7.1 Nickel in Urease

Nickel is required for the synthesis of active urease in plant and other cells. The enzyme catalyzes the hydrolysis of urea to carbon dioxide and ammonia, *via* the intermediate formation of carbamate ion (equation 46). The molecular weight has been redetermined recently[875] as $590\,000 \pm 30\,000$, with six subunits. Each subunit has two nickel centres and binds one mole of substrate. The activity of the enzyme is directly proportional to the nickel content, suggesting an essential role for nickel in the enzyme. Several approaches, including EXAFS measurements,[876] suggest that histidine residues provide some ligands to nickel, and that the geometry is distorted octahedral. There appears to be a role for a unique cysteine residue in each subunit out of the 15 groups present. Covalent modification of this residue blocks the activity of the enzyme.

$$(NH_2)_2CO + H_2O \rightarrow CO_2 + 2NH_3 \quad (46)$$

On the basis of kinetic studies on model compounds, it has been suggested that urea is *O*-coordinated to the nickel(II), which functions as a Lewis acid in the activation of urea towards

attack on the carbon of the substrate by a hydroxide residue coordinated to the second Ni^{II} centre. The unique cysteine residue is suggested to act as a general acid to promote loss of ammonia. This is represented schematically in Figure 33. It remains to be confirmed that the two Ni^{II} ions in the subunit are close together, probably no more than 6 Å apart, for this scheme to be viable.

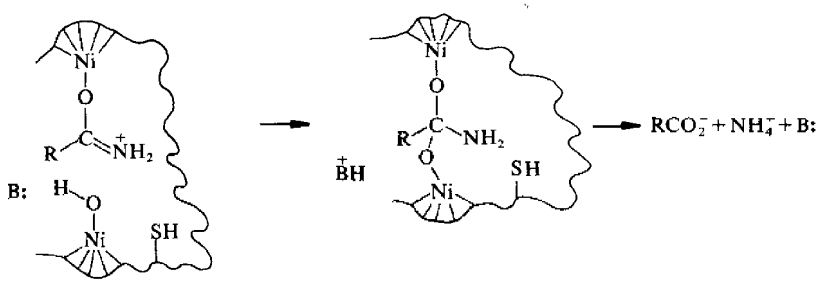


Figure 33 The mechanism of action of urease

62.1.7.2 Nickel in Methanogenic Bacteria. Factor F430

The requirement for nickel by methanogenic bacteria was long overlooked, partly because the stainless steel needles used in the anaerobic culture technique allowed enough nickel to dissolve to sustain growth. A yellow, low molecular weight nickel-containing compound with an absorption maximum at 430 nm and $\varepsilon = 22\,800\ dm^3\ mol^{-1}\ cm^{-1}$ has been isolated from these bacteria. This factor (F430) is the prosthetic group of methyl coenzyme M reductase, which catalyzes the conversion of methyl cofactor M into methane (equation 42).[877]

Factor 430 appears to be a nickel tetrapyrrole. Thus biosynthetic experiments have demonstrated the incorporation into F430 of δ-aminolevulinic acid. Detailed NMR studies on the product of methanolysis of F430 have led[878] to the postulate of a hydroporphyrin structure for F430M, as shown in Figure 34. This structure has not been previously found among natural porphinoids. It contains structural elements of both porphyrins and corrins but is less extensively conjugated, and the chromophore skeleton contains an additional carbocyclic ring. The NMR studies suggest that the ring is buckled to a substantial extent. This will allow stronger interaction between Ni^{2+} and the nitrogen donor atoms of the corphin structure.

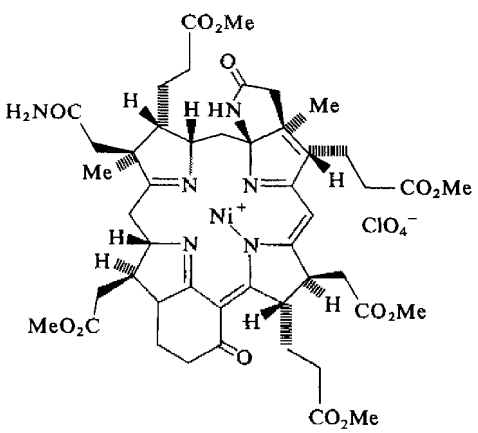


Figure 34 The structure of factor 430M

The parent compound F430 has now been confirmed to have the pentaacid structure implied from the structure of F430M shown in Figure 34. Factor 430 occurs protein-bound and protein-free in cells of *Methanobacterium thermoautotrophicum*.[879,880] In the former case, it is bound to methyl coenzyme M reductase in 2:1 ratio of F430 to protein. The two forms of the cofactor appear to be identical. This situation may result from overproduction of the corphinoid in the protein-free state in response to higher levels of nickel in the growth medium. The protein-free F430 can then be incorporated into methyl cofactor M reductase as required. It is interesting to speculate if the

nickel is linked to the protein through an axial ligand provided by the protein, but nothing is really known about this at present.

Factor 430M is diamagnetic in inert solvents, suggesting the presence of a square planar Ni^{II} centre. It is paramagnetic when dissolved in a mixture of water and methanol, suggesting that water is coordinated either in both axial positions to give an octahedral complex, or in one position only to give a five-coordinate complex with the nickel out of the plane.

Methyl cofactor M reductase has a molecular weight of about 300 000, and contains three pairs of subunits, all having different molecular weights. Factor 430 is obtained from the enzyme by boiling with 40% aqueous ethanol, or by extraction with perchloric acid at pH 2. The latter process gives two products, a yellow F430II, and a red F560, which contains an extra absorption band at 560 nm. While F430 has a molecular weight of about 1000, the extracted species may have higher molecular weights up to about 1500. This is due to the presence of additional molecules associated with the cofactor, such as cofactor M, or cofactor M plus a spacer group, or a nitrogenous base which may be present as an axial ligand. Factor 430 is highly reduced, and while it is stabilized with respect to oxidation, it will undergo reaction to give a number of products.

Methanogens contain at least two other nickel enzymes, namely hydrogenase (Section 62.1.7.4) and carbon monoxide dehydrogenase. Carbon monoxide dehydrogenases from acetogenic bacteria are better known (Section 62.1.7.3) but two examples from methanogenic bacteria have now been characterized, namely from *Methanosarcina barkerii*[881] and *Methanobrevibacter arboriphilicus*.[882] These two enzymes are also involved in acetate metabolism but have low affinity for CO ($K_m \approx 5$ mmol dm^{-3}) compared to enzymes from organisms that grow readily on CO ($K_m \approx 12$ μmol dm^{-3}). Although *M. barkerii* can grow poorly on carbon monoxide as the sole carbon and energy source, it appears unlikely that the primary function of the CO dehydrogenase is associated with the reactions of carbon monoxide.

Studies[883] on the uptake of Ni^{2+} by *M. bryantii* have demonstrated the presence of a highly specific uptake system with $K_m = 3.1$ μmol dm^{-3}. This pathway was not affected by high levels of other metal cations, including Mg^{2+} but with the exception of Co^{2+}. Transport of Ni^{2+} is coupled to movement of protons. Usually uptake of Ni^{2+} into bacteria occurs by the transport process for magnesium, not surprisingly in view of their similar ionic radii. It is appropriate, therefore, that an organism such as *M. bryantii* which has a specific requirement for Ni^{2+} should have a specific transport system for its uptake.

62.1.7.3 Nickel in Carbon Monoxide Dehydrogenase from Acetogenic Bacteria

Carbon monoxide is a substrate for a number of bacteria. It serves as the sole carbon and energy source under aerobic conditions for the carboxydo bacteria, which have a molybdenum-containing carbon monoxide oxidase. Carbon monoxide is used under anaerobic conditions by acetogenic bacteria, such as *Acetobacterium woodii*, *Clostridium thermoaceticum* and *Clostridium pasteurianum*, which require nickel for the synthesis and function of carbon monoxide dehydrogenase. These acetogenic bacteria can form acetate from CO_2, in which the methyl group of the acetate is formed from CO_2 by reduction *via* formate and one-carbon derivatives of H_4folate. They can also be grown on carbon monoxide, which may be oxidized to CO_2 by carbon monoxide dehydrogenase or converted into acetate.

Carbon monoxide dehydrogenase has been isolated from several acetogenic bacteria and purified in some cases, as shown in Table 20. This also contains details of carbon monoxide dehydrogenases from methanogens. The enzymes from *C. thermoaceticum*[884] and *A. woodii*[885] have been compared. They both have molecular weights about 450 000 with six subunits, $(\alpha\beta)_3$, but can exist as dimers, $\alpha\beta$. The larger subunits appear to be identical in both cases, but the smaller ones differ. Nickel is present in concentrations that suggest two Ni per molecule of dimeric enzyme. There also appear to be two or three [4Fe-4S] clusters per dimeric enzyme, while the *A. woodii* enzyme may have a 3Fe centre.

It is suggested that the nickel is bound to a low molecular weight factor, different from F430 of methanogens, and which may involve a corrinoid structure. The nickel is thought to cycle between Ni^{II} and Ni^{III}, with the CO bound to the metal. ESR data have been interpreted in terms of an Ni^{III} species with a bound radical derived from either CO or CO_2.[886] The involvement of a nickel-carbon bond has been unequivocally established by isotopic substitution (which is shown in the $g = 2.08$, 2.02 signals). About 40% of the total nickel is present as this species, suggesting that the Ni—C species is a viable intermediate in the catalytic conversion of CO to CO_2. There are parallels with industrial and laboratory catalytic processes, but the involvement of Ni^{III} seems

Table 20 Some Carbon Monoxide Dehydrogenases

Source	MW	Subunits	Metal/hexamer Ni	Fe	Zn	Labile sulfide	Ref.
Methanogens							
Methanosarcina barkerii	232 000 ($\alpha_2\beta_2$)	92 000 18 000	Yes				1
Methanobrevibacter arboriphilicus	140 000		Yes				2
Acetogens							
Clostridium thermoaceticum	440 000 $(\alpha\beta)_3$	77 600 70 900	6	32	3	42	3
Acetobacterium woodii	480 000 $(\alpha\beta)_3$	80 000 68 000	5	27	Varies	36	4
Clostridium pasteurianum			Yes				5

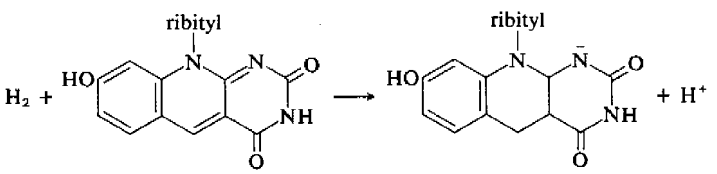
1. J. A. Krzycki and J. G. Zeikus, *J. Bacteriol.*, 1984, **158**, 231.
2. K. E. Hammel, K. L. Cornwell, G. B. Diekert and R. K. Thauer, *J. Bacteriol.*, 1984, **157**, 975.
3. S. W. Ragsdale, J. E. Clark, L. G. Ljungdahl, L. L. Lundie and H. L. Drake, *J. Biol. Chem.*, 1983, **258**, 2364.
4. S. W. Ragsdale, L. G. Ljungdahl and D. V. DerVartanian, *J. Bacteriol.*, 1983, **155**, 1224.
5. H. L. Drake, *J. Bacteriol.*, 1982, **149**, 561.

unusual. Electron transfer from Ni^{II} could generate a carbon monoxide radical anion. Electrophilic attack by a proton upon the oxygen atom would enhance nucleophilic attack of hydroxide upon the carbon, with the formation of a formate radical species. This could either decompose or be incorporated into acetate synthesis.

62.1.7.4 Nickel in Hydrogenase

Nickel is not an essential requirement for all hydrogenase activity, as it is not present in every hydrogenase. Nevertheless it is appreciated[873] now that an increasing number of hydrogenases do require nickel. Hydrogenases also contain iron–sulfur centres, generally of from four to 12 iron atoms, representing two-, three- and four-iron structures. The techniques of ESR and Mössbauer spectroscopy have been particularly useful in studying these proteins. ESR is an important and sensitive tool for detecting and characterizing nickel centres, while Mössbauer spectra show the presence of diamagnetic iron–sulfur clusters.

Nickel in hydrogenase is bound to protein, and is suggested to cycle between Ni^{II} and Ni^{III} during reaction with substrate dihydrogen. The original assignment to Ni^{III} arose from a consideration of ESR signals at $g = 2.30$, 2.23 and 2.02. The g values eliminated iron–sulfur centres as the paramagnetic centres responsible for the signals, and suggested rather a low-spin d^7 configuration. Lancaster[887] noted that the lack of nuclear hyperfine structure eliminated Co^{II}, and suggested that the paramagnetic centre was low-spin Ni^{III} in a rhombically distorted octahedral environment. This suggestion would probably not have been made on chemical grounds, but receives support from the ESR spectra of model compounds with Ni^{III}. The now-characteristic nickel ESR signals were then observed for hydrogenase from, for example, *M. thermoautotrophicium*, *M. bryantii* and *Desulfovibrio gigas*.[888] Conclusive support for the presence of Ni^{III} came from studies on hydrogenase isolated from *M. thermoautotrophicum*[889] and from *D. gigas*[890] grown on media enriched in $^{61}Ni^{2+}$, an isotope with a nuclear spin of $\frac{3}{2}$, and observing the expected hyperfine splitting in the ESR spectra. Some details of hydrogenases containing nickel are given in Table 21. In some cases additional cofactors are necessary. One hydrogenase from *M. thermoautotrophicum* uses factor 420 as a substrate. This is 8-hydroxy-5-deazaflavin, which is an acceptor of dihydrogen-derived electrons, subsequently transferring them to molecules such as carbon dioxide (equation 47).



(47)

Table 21 Some Nickel-containing Hydrogenases

Source	*MW*	*Ni* (mol)	*Fe* (mol)	*Clusters*	*Others*	*Ref.*
D. gigas	89 000	1	11/12	[3Fe-*x*S] 2 [4Fe-4S]		1
M. thermoautotrophicum						
F420-reducing	170 000	2.5–3	33–43		2–3 FAD	2
Methylviologen-reducing		1 (ratio)	15/20			
D. desulfuricans		0.7	11	[3Fe-4S] 2 [4Fe-4S]		3
C. vinosum		+	7	[3Fe-*x*S] [4Fe-4S]		4
A. eutrophus		1–2		2 [4Fe-4S] 2 [2Fe-2S]	FMN	5
Methanosarcina barkerii		0.5		2 [4Fe-4S]	FMN	1
Nocardia opaca 1b	200 000					6

1. J. J. G. Moura, M. Teixeira, I. Moura and A. V. Xavier, *J. Mol. Catal.*, 1984, **23**, 263.
2. N. Kojima, J. A. Fox, R. P. Hausinger, L. Daniels, W. H. Orme-Johnson and C. Walsh, *Proc. Natl. Acad. Sci. USA*, 1983, **80**, 378.
3. H. J. Kruger, B. H. Huynh, P. O. Ljungdahl, A. V. Xavier, D. V. DerVartanian, I. Moura, H. D. Peck, M. Teixeira, J. J. G. Moura and J. LeGall, *J. Biol. Chem.*, 1982, **257**, 14620.
4. S. P. J. Albracht, M. L. Kalkman and E. C. Slater, *Biochim. Biophys. Acta*, 1983, **724**, 309.
5. C. Friedrich, K. Schneider and B. Friedrich, *J. Bacteriol.*, 1982, **152**, 42; K. Schneider, R. Cammack, H. G. Schlegel and D. O. Hall, *Biochim. Biophys. Acta*, 1979, **578**, 445.
6. K. Schneider, H. G. Schlegel and K. Jochim, *Eur. J. Biochem.*, 1984, **138**, 533.

As noted in Table 21, *M. thermoautotrophicum* produces two hydrogenases containing nickel and iron.[891,892] The environment in the F_{420}-reducing hydrogenase in a stable oxidized state has been partially clarified by use of electron spin echo[893] and EXAFS spectroscopy.[894] EXAFS data could be fitted to sulfur but not to nitrogen or oxygen donor atoms. It is concluded that sulfur is the dominant scatterer in the nickel EXAFS of the F_{420}-reducing hydrogenase, with three sulfur atoms at about 2.25 Å. A nitrogen atom has been detected at ≥3.5 Å from the nickel site by electron spin echo spectroscopy, but this was not detected in the EXAFS studies. It is suggested tentatively that the nickel has equatorial sulfur donors with either one or two loosely held axial ligands in either a tetragonally distorted octahedron or a square pyramid. Previous ESR studies have suggested the presence of low-spin Ni^{III} with the unpaired electron in an orbital of d_{z^2} symmetry, in accord with this proposal.

The second hydrogenase from *M. thermoautotrophicum* does not catalyze the reduction of F_{420}, but only the artificial one-electron acceptor methylviologen. This hydrogenase does not appear to have the nitrogen atom near the nickel centre, as found for the F_{420}-reducing hydrogenase.[893] However, the latter hydrogenase has one equivalent of bound FAD, which seems to be absent from the viologen-reducing enzyme. This FAD could be coordinated to the nickel, so accounting for the additional nitrogen ligand.

It appears that the Ni^{III} signal observed initially is associated with an inactive form of hydrogenase. Reduction, with loss of Ni^{III}, is required before catalytic activity is regained. Thus, detailed studies on *D. gigas* hydrogenase show that the ESR spectrum changes as the enzyme is incubated with H_2. The Ni^{III} signal is lost. A transient radical type of signal appears next, and its disappearance is accompanied by the reappearance of a different Ni^{III} signal, with *g* values 2.19, 2.16 and 2.02, which then disappears.[890] Evidence for a transient Ni^{III} signal was also found in hydrogenase from *M. thermoautotrophicum* (ΔH strain). Removal of H_2 from the enzyme and replacement with argon result in the recovery of the Ni^{III} signal. This confirms that the nickel centre is able to participate in the transport of electrons between the various redox centres in the enzyme.[891] Indeed there is some evidence that Ni^{III} and a $[4Fe\text{-}4S]^{3+}$ cluster interact magnetically in the hydrogenase from *Chromatium vinosum*.[895]

Some evidence to support the catalytic involvement of nickel in the binding of dihydrogen comes from a comparison with reduction by dithionite. In the latter case, the various centres of *D. gigas* hydrogenase are reduced in order of decreasing midpoint reduction potentials. Under an atmosphere of H_2, the nickel centre is reduced preferentially.

A complication arises from a consideration of potentials. The midpoint reduction potentials of model peptide complexes of Ni^{III}, which appear to involve deprotonated peptide donor sites, lie between +0.79 and +0.96 V. These values are much greater than the values found for the Ni^{III}/Ni^{II} couple of the hydrogenase from *D. gigas* (−0.145[888] or −0.220 V[890]). An obvious conclusion is that nickel in hydrogenase is bound by different amino acid groups from those involved in the

model complexes. A comparison of the ESR spectra of Ni^{III} complexes with the peptides *N*-mercaptoacetylglycyl-L-histidine and *N*-mercaptoacetylglycylglycylglycine with that of the Ni^{III} centre in hydrogenase has led[896] to the suggestion that the nickel in hydrogenase contains one cysteine residue in its coordination environment.

The potential of the Ni^{III}/Ni^{II} couple in hydrogenase is higher than the $2H^+/H_2$ couple by about 0.2 V, so there are mechanistic difficulties in postulating a role for Ni^{III}/Ni^{II} in the activation of dihydrogen. It is important that further measurements be made on midpoint potentials for nickel in various hydrogenases to check that these values relate to mechanistically important species.

It should also be noted that only close to 50% of the total nickel is present as Ni^{III}. The simplest explanation is that there is a second ESR-undetectable nickel. This nickel centre may have an important role in the activity of hydrogenase. Its structural relationship to the ESR-detectable nickel is of great interest. Some type of nickel dimer cannot be ruled out completely.

62.1.7.5 Uptake of Nickel by Plants

Certain plants accumulate[897] very high levels of nickel in their tissues: *Hybanthus floribundus* contains up to 1.3% nickel on a dry mass basis, while *Psychotria douarrei* has up to 44% nickel in the plant ash. *Allysum* is also known as a nickel accumulator. A large part of the nickel in these plants is water soluble, and in the last case is associated with malic and malonic acids.[898] In *Hybanthus floribundus*, the nickel is largely accumulated in the leaves, where it is associated with pectic carbohydrates.

62.1.8 THE BIOCHEMISTRY OF COPPER

Copper is widely distributed at trace levels in living systems. Highest levels in man are found in the liver, brain, lung and kidney in decreasing amounts. High concentrations are also found in pigmented parts of the eye associated with melanins. High levels of copper are associated with certain diseased states, notably Wilson's disease (hepatolenticular degeneration). Menke's disease is an inborn error of copper metabolism that leads to a life expectancy of less than three years, and where the clinical symptoms can be accounted for largely in terms of low activity of copper-requiring enzymes. The major lethal effect is copper deficiency in the brain. A characteristic feature of Menke's disease is a "kinky" hair structure.

Copper has an essential role in a number of enzymes, notably those involved in the catalysis of electron transfer and in the transport of dioxygen and the catalysis of its reactions. The latter topic is discussed in Section 62.1.12. Hemocyanin, the copper-containing dioxygen carrier, is considered in Section 62.1.12.3.8, while the important role of copper in oxidases is exemplified in cytochrome oxidase, the terminal member of the mitochondrial electron-transfer chain (62.1.12.4), the multicopper blue oxidases such as laccase, ascorbate oxidase and ceruloplasmin (62.1.12.6) and the non-blue oxidases (62.12.7). Copper is also involved in the Cu/Zn-superoxide dismutases (62.1.12.8.1) and a number of hydroxylases, such as tyrosinase (62.1.12.11.2) and dopamine-β-hydroxylase (62.1.12.11.3). Tyrosinase and hemocyanin have similar binuclear copper centres.

Copper is also present in a number of small proteins, characterized by an intense blue colour, that catalyze the transfer of electrons. These blue electron-transfer proteins will be discussed in this section, while attention will be drawn, in summary, to the important structural aspects of the active sites of the copper proteins associated with the biochemistry of dioxygen.

Many reviews are available on the general biochemistry of copper,[899–905] electronic aspects of active sites[906,907] and relevant model chemistry of simple copper complexes.[908,909]

62.1.8.1 Types of Copper Centre

The copper centres in the multicopper blue oxidases have been classified into three groups. This classification may be extended to include other copper proteins.

62.1.8.1.1 Type 1 copper

This is the copper centre responsible for the deep blue colour of the blue oxidases and the blue electron-transfer proteins. Type 1 copper centres have an intense absorption band near 600 nm,

with an extinction coefficient about 100 times larger than those commonly found for coordination complexes of Cu^{II}, together with other absorptions at about 450 and 750 nm. A great deal of effort has been put into the synthesis of Cu^{II} complexes showing such features.

The ESR spectrum of the type 1 centre has small hyperfine coupling constants.

62.1.8.1.2 Type 2 copper

This centre, present in the multicopper blue oxidases, is similar to the typical Cu^{II} sites of tetragonal geometry found in simple coordination complexes of copper. It is ESR-active and has a normal d–d spectrum, which is difficult to measure in the presence of type 1 Cu due to its intense absorptions. The copper in the non-blue oxidases is often regarded as type 2 copper, although this was not implied by the original definition.

62.1.8.1.3 Type 3 copper

This centre consists of a pair of Cu^{II} ions, which are diamagnetic as a result of antiferromagnetic interaction. It is characterized by a strong absorption at around 330 nm with extinction coefficients in the range 3000 to 5000 $dm^3\ mol^{-1}\ cm^{-1}$. The type 3 centre is associated with redox reactions of dioxygen, as it can transfer two electrons and so bypass the formation of reactive superoxide. A number of model systems for type 3 copper have been reported.

62.1.8.1.4 Blue copper proteins

These are listed in Table 22, which includes details of the electron-transfer proteins and the blue oxidases.

Table 22 Blue Copper Proteins

Protein	*MW*	*Type 1* ($E°$) (mV)	*Type 2* ($E°$) (mV)	*Type 3* ($E°$) (mV)
Stellacyanin	20 000	1 (184)		
Rusticyanin	16 500	1 (680)		
Umecyanin	14 600	1 (283)		
Azurin	14 000	1 (328)		
Plastocyanin	10 500	1 (350–395)		
Plantacyanin	8000	1		
Mung bean blue		1		
Rice bran blue		1 (275)		
Laccase (fungal)	60 000–120 000	1 (785)	1	2 (782)
Laccase (*Rhus*)		1 (394)	1 (365)	2 (434)
Ceruloplasmin	130 000	2 (580, 490)	1	4
Ascorbate oxidase	150 000	2	2	4

62.1.8.2 The Blue Electron-transfer Proteins

These low molecular weight proteins have been isolated from a variety of sources. They cycle between Cu^{II} and Cu^{I}.[910]

62.1.8.2.1 Plastocyanins

The plastocyanins are found in plant chloroplasts and other photosynthetic organisms, and act as membrane-bound electron carriers between photosystems II and I in the photosynthetic pathway of higher plants, green algae and some blue-green algae.

Plastocyanin consists of a single polypeptide chain of molecular weight around 10 500 and one copper atom. It is synthesized in the cytoplasm as a precursor of higher molecular weight,[911] with an additional polypeptide that is essential for transport of the protein into the chloroplast. Within

the chloroplast the apoplastocyanin is formed and binds copper. In the case of the green alga *Scenedesmus acutus*, both the 14 000 molecular weight precursor and the apoplastocyanin accumulate in significant amounts when the alga is grown in a copper-deficient growth medium.[912]

Amino acid sequence data for many plastocyanins are now available. A large number of residues are conserved,[910] particularly among the plastocyanins from higher plants, where about 50% of the residues are the same. Residues 31–44 and 84–93 are highly conserved in all the proteins, and provide the donor groups for copper.

The crystal structure of oxidized poplar plastocyanin has now been refined to 1.6 Å resolution.[913] The protein is cylinder-like in overall structure, with dimensions of $40 \times 32 \times 28$ Å^3, and with the metal ion site buried 6 Å in the interior towards one end. The copper site, shown in Figure 35, involves as ligands the imidazole groups of His-37 and His-87 (2.10 Å), and the sulfur atoms of Cys-84 (Cu—S = 2.13 Å) and Met-92 (Cu—S = 2.90 Å). The second N in the imidazole of His-87 is hydrogen bonded to a water molecule. The geometry of the metal site is irregular, approximating to distorted tetrahedral with bond angles differing by up to 50° from tetrahedral geometry.

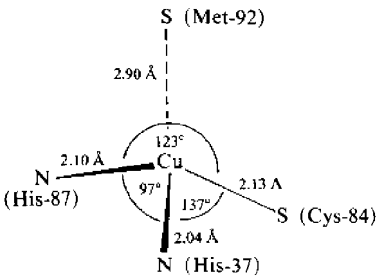


Figure 35 Schematic representation of the active site structure of poplar plastocyanin

The structure of the reduced protein[903] involves displacement of the Cu atom by about 0.4 Å in a direction such that the Cu—S(Met) bond decreases to 2.74 Å, while the imidazole of His-87 is displaced about 0.4 Å away from the copper. The copper appears to move within the ligand cage.

The type 1 copper site thus provides a set of ligand donor atoms and a stereochemistry that is a compromise between the preferences of Cu^{I} (soft ligands and tetrahedral geometry) and Cu^{II} (hard ligands and square planar geometry). The structural restriction placed upon the copper by the protein results in a diminishing of the Franck–Condon reorganization barrier to electron transfer.

The essential role of the protein in this context is supported strongly by comparison with the structure of the apoplastocyanin, determined at 1.8 Å resolution.[914] The structures of apoplastocyanin and Cu-plastocyanin are very similar, showing that the irregular geomtry of the type 1 site is imposed upn the metal by the polypeptide. Only five residues in plastocyanin undergo

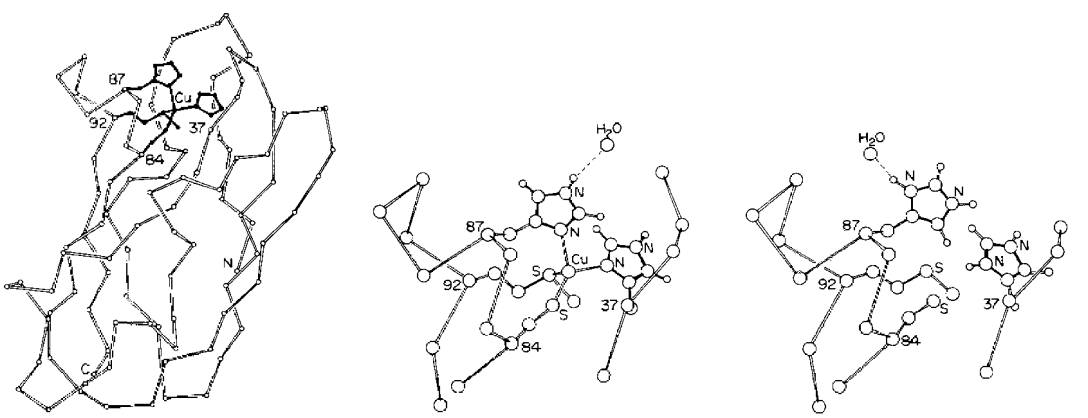


Figure 36 The structures of plastocyanin and apoplastocyanin (reproduced with permission from *J. Biol. Chem.*, 1984, **259**, 2822)

significant changes when the copper atom is removed. His-87 is one such residue. In this case, the orientation of the imidazole ring is changed by a rotation of 180° about the $C^{\beta}-C^{\gamma}$ bond. The N^{δ} atom of His-87 is then hydrogen bonded to a different water molecule from the one involved in the structure of Cu-plastocyanin (Figure 36). The imidazole ring of His-87 accordingly acts as a 'revolving door' to give access to the copper site. This is consistent with the two-stage mechanism previously postulated for the incorporation of Cu^{II} into apostellacyanin[915] and apoazurin.[916,917] The reversible binding of Cu^{II} at the exposed N^{δ} atom of His-87 will be followed by the rotation of the imidazole ring and the formation of the other three Cu-protein links.

The structure of plastocyanin offers several hydrophobic channels for the quantum mechanical tunnelling of electrons. However, residue His-87 provides a short pathway to the solvent and so an outer-sphere mechanism seems feasible. The protein surface contains two patches of highly conserved residues. One of these consists of two groups of acidic side-chains surrounding the exposed side-chain of a tyrosine, Tyr-83. The second patch is made up of hydrophobic side-chains surrounding the exposed edge of the imidazole ring of His-87. Both patches may be recognition or binding sites for redox partners, as noted earlier for its natural donor[709] cytochrome c_{552} (cytochrome *f*, Section 62.1.5.2.2) and for its acceptor, P700.

62.1.8.2.2 Azurin, stellacyanin and other type 1 sites

The azurins are electron-transfer proteins in the respiratory chains of certain bacteria. They have been particularly well studied from *Pseudomonas aeruginosa* and other pseudomonads, and contain one type 1 copper bound to a single polypeptide chain of molecular weight about 16 000. Amino acid sequence data for a number of azurins show that about one third of residues are conserved. All contain three cysteine residues. Three are also sequence homologies with the plastocyanins.

The structure of *Ps. aeruginosa* azurin has been determined by X-ray crystallography at low resolution[918] and by EXAFS techniques.[919] The structure is similar to that of plastocyanin, and involves two imidazoles from His-46 and His-117 (Cu—N = 1.97 Å) and sulfur atoms from Cys-112 and Met-121. Again, there is a short Cu—S(Cys) distance (2.10 Å) and a long Cu—S(Met) distance of 2.25 Å.

Stellacyanin from *Rhus vernicifera* is less well studied. The polypeptide does not contain a methionine residue showing that the ligands of the type 1 site may vary. There is EXAFS evidence for a short Cu—S(Cys) bond,[920] while UV, visible and near IR studies confirm similarities with the other blue proteins. It has been suggested that methionine is replaced as a ligand by an —S—S— group. This is based on resonance Raman[921] and NMR studies.[922]

The other small blue proteins are only poorly characterized at present. It is assumed their function is that of electron transfer. Rusticyanin from *Thiobacillus ferrooxidans* is thought to be the initial electron acceptor from iron(II) in the respiratory chain at pH 2. Rusticyanin contains 159 residues, with one cysteine, three methionine and five histidine residues. The protein is unusually stable at low pH, in accord with its presence in an acidophilic organism. The midpoint potential of rusticyanin is high (+680 mV), and is second in magnitude only to that of *Polyporus* laccase.

62.1.8.2.3 Spectroscopic studies on blue electron-transfer proteins

Considerable advances in the understanding of the electronic properties of the type 1 centre arose from the application of IR CD techniques to the question of the assignment of *d–d* bands of plastocyanin in a region usually dominated by vibrations of the protein.[923] Three bands at 11 200, 9000 and 5100 cm^{-1} were assigned as *d–d* absorptions in a distorted tetrahedral environment. The visible absorption bands could then be assigned to S-Cu charge transfer. These developments have been well reviewed.[906]

Additional information has been obtained from single crystal, polarized optical and ESR spectroscopic studies[924] on poplar plastocyanin, which have allowed a correlation of the electronic structure of the blue copper active site with its geometric structure. In summary, the three dominant absorption bands at 13 350, 16 490 and 17 870 cm^{-1} were assigned to CysS → Cu ($d_{x^2-y^2}$ charge-transfer transitions. The methionine makes only a small contribution, due to the long Cu—S(Met) bond (2.9 Å) and the poor overlap of the methionine sulfur orbitals with the $d_{x^2-y^2}$ orbital of copper. Histidine-Cu charge transfer contributes to the weaker absorptions at 21 390 and

23 340 cm^{-1}. The blue type 1 copper site in plastocyanin is suggested to be elongated C_{3v} symmetry with significant rhombic distortion.

Visible MCD spectra of plastocyanin, azurin, *Rhus vernicifera* laccase, ascorbate oxidase and ceruloplasmin are similar on a 'per copper' basis, but show differences from those of stellacyanin and fungal laccase. This is of interest in view of the absence of methionine from the coordination sphere of copper in stellacyanin, and the very high redox potential of fungal laccase.[925]

The resonance Raman spectra of azurin, stellacyanin and both tree and fungal laccase have been examined in detail.[926] Effects of removal of type 2 copper from laccase have also been noted. It appears that the dominant features of these spectra at around 400 cm^{-1} are not due to metal-ligand stretching modes. Only Cu—S(Cys) stretching is significantly involved in the ~400 cm^{-1} bands, while a component of a moderate intensity band at ~265 cm^{-1} is assigned to Cu—N(His) stretching. It appears that the Raman spectra are complicated by internal vibrational modes of the Cu ligands. For example, the SCC bend of the cysteine side-chain can couple strongly with the Cu—S stretch. This might account for a pair of strong bands in the Raman spectrum of stellacyanin, since each of them shows half of the $^{63}Cu/^{65}Cu$ shift expected for Cu—S(Cys) stretching. However, in laccase, these strong bands show substantially smaller $^{63}Cu/^{65}Cu$ shifts, probably reflecting different conformations of the protein ligands. One problem in interpreting the resonance Raman spectrum is accounting for the resonance enhancement of so many blue-site bands.

^1H NMR techniques have been widely applied to these blue proteins. Resonances have been assigned in the reduced azurin and plastocyanin and the varying effect of oxidation of the copper on the broadening of resonances noted. The identities of the ligands in azurin and plastocyanin were suggested[927] to be His-46, Cys-112, His-117 and Met-121, and His-37, Cys-84, His-87 and Met-92 respectively in agreement with the findings of the X-ray diffraction results. Water relaxation rates measured by ^1H NMR on *Chenopodium album* plastocyanin showed that the Cu^{II} was inaccessible to the solvent.

Several metals bind at the vacant copper site of apoazurin, including Ni^{II} and Co^{II},[928] and, less usually, gold.[929] There were some differences between the ^1H NMR spectra of the copper and gold azurins, notably in the methionine S—Me region. Au^I prefers linear coordination.

62.1.8.2.4 Electron-transfer reactions with inorganic complexes

It has been noted that the copper centres in the blue electron-transfer proteins are inaccessible to solvent, and that the possibility of an outer-sphere mechanism is favoured through the proximity to the surface of the protein of the imidazole groups of His-87 (in plastocyanin) and His-117 (in azurin). In the case of stellacyanin, one of the cysteine ligands is adjacent to an organic residue attached to a bulky carbohydrate and so may be accessible. Accordingly, reaction of these proteins with a range of inorganic outer-sphere redox reagents has been studied. The following reactions have been reported, in some cases conflicting results being obtained by different researchers: oxidation of plastocyanin(I) by $[Co(bipy)_3]^{3+}$,[930] $[Co(phen_3]^{3+}$,[930,931] $[Co(substituted\ phen)_3]^{3+}$,[932,933] $[Fe(CN)_6]^{3-}$,[930,934] $[Ru(NH_3)_5py]^{3+}$,[935] excited $[Ru(bipy)_3]^{2+}$;[936] reduction of plastocyanin(II) by $[Ru(NH_3)_5py]^{2+}$,[930] $[Fe(CN)_6]^{4-}$,[930,937] $[Fe(EDTA)]^{2-}$;[938,939] oxidation of azurin(I) by $[Ru(NH_3)_5py]^{3+}$,[935] $[Co(phen)_3]^{3+}$,[933,940] $[Co(substituted\ phen)_3]^{3+}$,[933,940] $[Fe(CN)_6]^{3-}$,[940,941] excited $[Ru(bipy)_3]^{2+}$;[936] reduction of azurin(II) by $[Fe(EDTA)]^{2-}$,[938,939] $[Fe(CN)_6]^{4-}$;[940,941] oxidation of stellacyanin(I) by $[Ru(NH_3)_5py]^{3+}$,[935] $[Co(phen)_3]^{3+}$,[933] $[Co(substituted\ phen)_3]^{3+}$,[933] $[Co(EDTA)]^-$,[942,943] various polyamine-carboxylate complexes of Co^{II},[944] Co^{III},[945] excited $[Ru(bipy)_3]^{2+}$,[936] $[Ru(en)_3]^{3+}$,[943] $[Co(C_2O_4)_3]^{3-}$;[943] reduction of stellacyanin(II) by $[Fe(EDTA)]^{4-}$.[938,939] Comparison of rate constants for equivalent reactions suggests that the order of kinetic accessibility to the copper site lies in the sequence stellacyanin > azurin > plastocyanin. This is based upon the assumption that the larger the spread of the self-exchange rate constant k_{11} values, the less kinetically accessible is the copper centre.

There are many instances for azurin and plastocyanin where limiting kinetic behaviour is observed, and attributed to the formation of an adduct between the protein and the inorganic complex followed by electron transfer. Values of the association constants and of the electron-transfer rate constants may then be calculated. This situation has not been observed in the case of stellacyanin, which differs from azurin and plastocyanin in that it has an overall positive charge at pH 7 (of +7 in the case of the reduced protein). The electron-transfer rate constants are often associated with fairly large negative values for the entropy of activation (in the range −84 to −210 $J\ K^{-1}\ mol^{-1}$), which are not expected for electron transfer within a compact assembly.

The observed second order rate constants, which will be a product of the association constant and the electron-transfer rate constant, will be pH dependent if a protonated form of the protein has a different reactivity from the unprotonated form. The oxidation of plastocyanin by a range of negatively charged complexes decreases with decrease in pH, the dependence of rate constant upon pH leading to a pK_a value of about 6. This may be interpreted simply in terms of the protonation of a residue close to the copper which normally binds the complex, but which is unable to do so when protonated. This residue could well be His-87. Oxidation of plastocyanin by $[Co(4,7\text{-}(O\text{-}SO_3)_2phen)_3]^{3-}$ is independent of pH in this pH region, suggesting that this oxidizing agent binds to a different site on the surface of the protein. This has been confirmed by blocking experiments with non-redox active complexes.[932] Thus, the oxidation by hexacyanoferrate(III) is blocked by $[Co(C_2O_4)_3]^{3-}$ at a site close to His-87. The oxidation of stellacyanin, surprisingly, is independent of pH over the pH range 5–10.[943]

Quenching of excited-state $[Ru(bipy)_3]^{3+}$ by reduced blue proteins involves electron transfer from the Cu^I with rate constants close to the diffusion limit for electron-transfer reactions in aqueous solution. It is suggested that the excited Ru^{II} complex binds close to the copper–histidine centre, and that outer-sphere electron transfer occurs from Cu^I through the imidazole groups to Ru^{2+}. Estimated electron-transfer distances are about 3.3 Å for plastocyanin and 3.8 Å for azurin, suggesting that the hydrophobic bipy ligands of Ru^{2+} penetrate the residues that isolate the Cu–His unit from the solvent.[936]

Reduction of rusticyanin by iron(II) and by chromium(II) has been reported.[945a] The former reaction shows effects due to anions, with limiting zero order kinetics observed in the presence of sulfate.

62.1.8.2.5 Electron-transfer reactions with proteins

Many of the reactions of the plastocyanins and azurins with other redox proteins follow Marcus behaviour.[946] These reactions all show a single mechanism of electron transfer, with no kinetic selectivity and no specific interactions between the proteins. The notable exception to this behaviour is cytochrome *f* (c_{552}), where a specific interaction occurs,[934] appropriate for its natural redox partner. Equation (48) represents a probable sequence of electron carriers, although it is difficult to extrapolate conclusions to the membrane-bound proteins.

$$\text{plastoquinone} \rightarrow \text{cytochrome } f \rightarrow \text{plastocyanin} \rightarrow \text{chlorophyll } a_1\ (\text{P700}) \qquad (48)$$

Azurin is involved in the electron-transfer chain to cytochrome oxidase in bacterial respiration. Reduction of oxidized azurin by cytochrome c_{551} is very fast,[946,947] but the reverse process is complicated through the existence of a slow conformational equilibrium.

62.1.8.2.6 Model studies for the type 1 site

Before the elucidation of the structural details of the type 1 site, a range of studies on the blue proteins[921,927,948–950] and on model compounds[951–955] had led to proposals that methionine, cysteine and two histidine residues were ligands for copper in azurin and plastocyanin. The question of the Franck–Condon barrier to electron transfer in small copper complexes has been explored. Electron transfer is slow in copper complexes of some N and O donor ligands,[956] and the rate is not accelerated by the presence of one or two thioether ligands,[957] showing that geometric factors are important in this context. The redox potentials of a range of complexes with varying numbers of sulfur donor atoms imply[957] that a model complex with two sulfur and two heterocyclic nitrogen donors should have a redox potential of about 600 mV, which will be increased by a further 50 to 200 mV by the low dielectric constant at the active site of a protein, and by a further amount (upwards of 300 mV) by imposition of tetrahedral geometry on the Cu^{II} centre. This leads to the suggestion that the type 1 site should be expected to have redox potentials of about 900 mV. The values given in Table 22 show that such high values are found in some cases. It is necessary therefore to explain the low value of stellocyanin (184 mV) rather than the high value of fungal laccase (785 mV). Suitable explanations could involve detailed geometric considerations.

62.1.8.3 The Type 3 Binuclear Copper Centre

The type 3 centre is present in the blue oxidases, and in hemocyanin, tyrosine and dopamine β-hydroxylase. Cytochrome oxidase, like laccase, contains four metal centres including an antiferromagnetically linked Fe···Cu pair. It appears that there are considerable similarities between the type 3 site and the cytochrome a_3···Cu_B site in cytochrome oxidase.

While this section is concerned with structural aspects of the type 3 site, there will be some overlap with the discussion of the blue oxidases, notably laccase, presented in Section 62.1.12.6.

Laccase contains one type 1 Cu and one type 2 Cu in addition to the type 3 pair. The copper can be reversibly removed from the type 2 site (to give T2D-laccase). Reconstitution may be accomplished by adding $CuSO_4$ or Cu^I under anaerobic conditions.[958] Loss of type 2 copper has little effect on the redox potentials of the type 1 and type 3 copper, or on the electron-transfer reactivity of the type 1 copper. It appears that type 2 Cu is a substrate-binding site in the reduction pathway for the blue copper.[959]

As noted above, the type 3 site has similarities to the cyt a_3···Cu_B pair in cytochrome oxidase. Both pairs function as O_2-reducing centres and are ESR-silent due to antiferromagnetic interactions in the oxidized and fully reduced enzymes. ESR signals have now been detected from the type 3 Cu^{II} in laccase intermediates in which the second Cu has been reduced to Cu^I.[960,961] Similarly, the ESR-silent Cu_B^{II} in cytochrome oxidase has been detected in an intermediate species. The ESR signals for the type 3 Cu in laccase and the Cu_B^{II} in cytochrome oxidase are very similar.

The Cu^{II} in the type 3 pair that becomes detectable on reduction of the other Cu^{II} has been studied by ENDOR techniques,[962] which show that the copper is coordinated by at least three nitrogenous ligands, at least one of which is an imidazole. All three ligands could be imidazoles. The fourth ligand appears to be an aqua or a hydroxo group. This could be a replacement for the ligand that normally bridges the two Cu^{II} centres of the type 3 site, and which remains with the Cu^I in the uncoupled state. Alternatively, the aqua group could be an exchangeable ligand for O_2 or O_2^-, and the bridge is an imidazole group, as known for the Cu/Zn superoxide dismutase, which has remained with the Cu^{II} centre. ENDOR measurements on cytochrome oxidase Cu_B^{II} confirm the similarity with the type 3 Cu in laccase.

62.1.8.3.1 Models for binuclear copper centres

Many binuclear copper complexes have been synthesized as models for binuclear sites in enzymes.[963] The strong antiferromagnetic interactions present in the natural binuclear copper centres probably result from a superexchange mechanism *via* bridging ligands. Imidazolate bridges are unable to give strong antiferromagnetic interactions in model systems.[964] Models involving thioethers have been proposed frequently to account for the high redox potentials of laccase, and also for the characteristic 330 nm band of type 3 Cu.[965] These models seem less likely to be valid now in view of the results described in the previous section.

Macrocyclic ligands or dinucleating ligands have also been used to bring two copper centres into close proximity (3–4 Å). Other requirements seem to be the presence of perhaps three nitrogen donors and effective bridging for antiferromagnetic interactions. Some of these ligands are shown in Figure 37. Ligand (**1**) is an amide ligand that undergoes ionization of the amide group on coordination.[966] Compound (**2**)[967] forms a dicopper complex in which each Cu^{II} ion is bonded to two imino nitrogens of the macrocycle, a thiocyanate group and to two bridging ethoxide groups in an approximately trigonal bipyramidal geometry. The Cu···Cu distance is 3.003 Å, and the pairs of Cu^{II} are strongly antiferromagnetically coupled (with $2J$ in the range -600 to $-700\ cm^{-1}$). The dicopper(II) complexes undergo reduction by heating their solutions in acetonitrile. These complexes catalyzed the oxidation of substrates such as catechols, hydroquinone and ascorbic acid.

Imidazolate-bridged dicopper(II) complexes of ligand (**3**) involve[968] the Cu^{II} centres being strongly bound in a planar geometry to three nitrogen atoms of the macrocycle and to one nitrogen atom of the bridging imidazolate group, and weakly bound to axial oxygen ligands (ClO_4^- or H_2O). Magnetic susceptibility measurements confirm antiferromagnetic interaction between the two copper centres with $2J$ about $-50\ cm^{-1}$.

Ligand (**4**) binds two Cu ions with a bridging phenoxide oxygen, with a pyramidal geometry around each Cu^I,[969] and a Cu···Cu separation of 3.6–3.7 Å. This ligand mimics the dioxygen reactivity found in the monooxygenases. The binuclear complex of the triketonate ligand (**5**) is

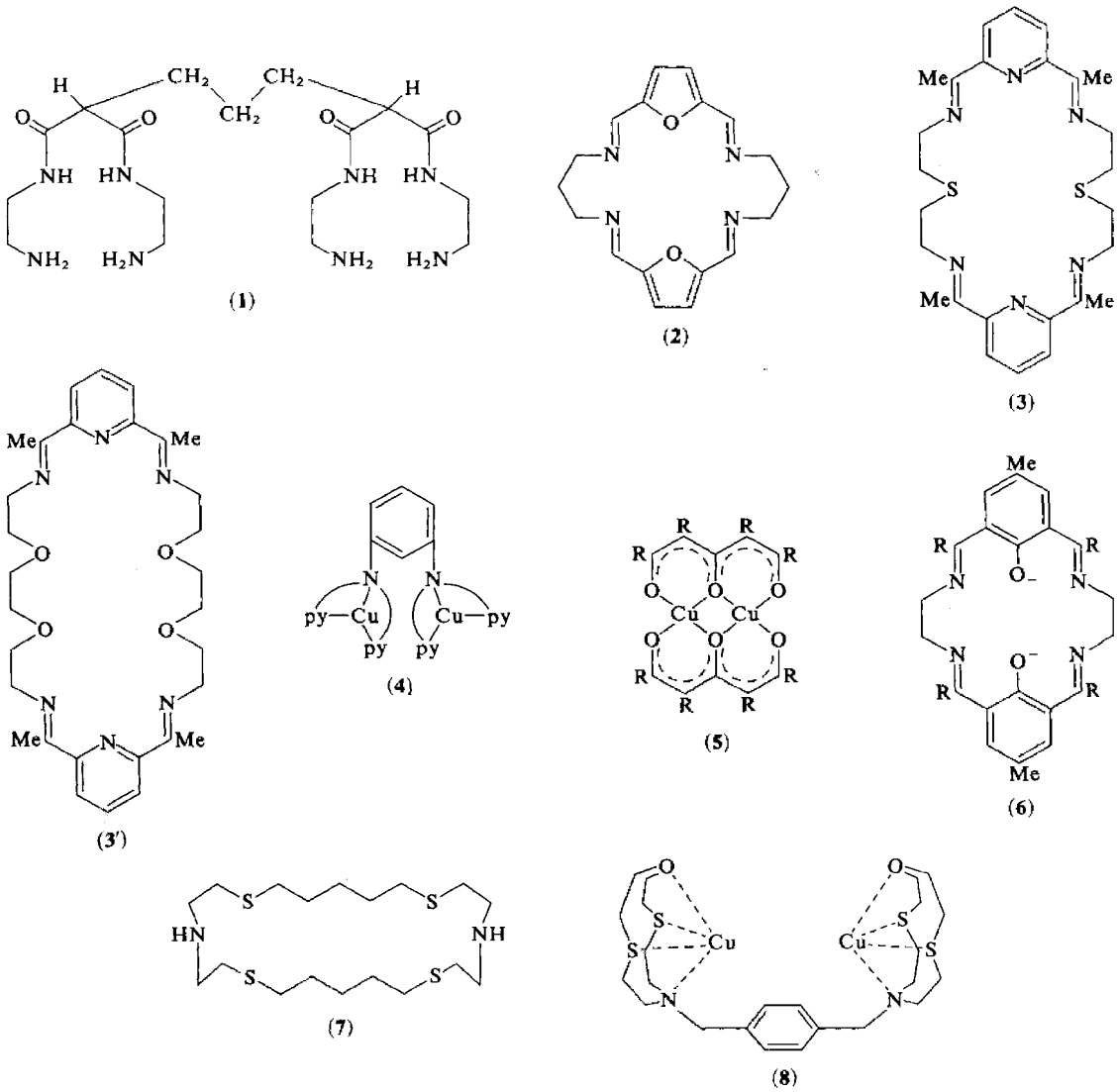


Figure 37 Model compounds for the type 3 copper site

diamagnetic at room temperature with $-2J = 740\ cm^{-1}$. The Cu^{II} centres can be reduced sequentially, but the redox potentials (−220 to −410 mV) are too low to mimic type 3 sites.[970]

The binuclear Cu^{II} complex of ligand (**6**) shows strong antiferromagnetic interactions with $-2J = 588\ cm^{-1}$.[971,972] Similar ligands have been reviewed.[963] Finally, the binuclear complex of ligand (7), with two bridging azide groups, is completely diamagnetic,[973] and ligand (**8**) acts as a carrier of O_2.[974]

62.1.8.4 The Type 2 Copper Centre

The paramagnetic copper present in the non-blue oxidases such as galactose oxidase and amine oxidases, and also in the blue oxidases, has *d*-*d* and ESR spectra typical of coordination complexes of copper(II).

ESR spectra of type 2 Cu suggest the presence of three to four nitrogen ligands, while bound water has also been implicated by proton relaxation rate measurements. A number of anionic inhibitors bind to type 2 Cu. These results suggest that substrates may bind to the type 2 copper centres in oxidases.

62.1.8.5 Ceruloplasmin

This blue oxidase, present in the plasma of vertebrates, appears to be multifunctional.[905,975] It accounts for some 95% of the circulating copper in a normal mammal, and its concentration fluctuates considerably in diseased states. It appears that ceruloplasmin has a major role in copper transport (as discussed in Section 62.1.11). In addition it has oxidase activity towards three groups of substrates, although its physiological role is not known with certainty.

62.1.8.5.1 Oxidase activity of ceruloplasmin

This is directed particularly towards Fe^{II},[976] the substrate with the highest V_m and the lowest K_m values. Ceruloplasmin-catalyzed oxidation of Fe^{II} is 10–100 times faster than the non-enzymatic reaction, and ceruloplasmin appears to be the only effective ferrooxidase in human serum. This is linked to the control of iron mobilization by ceruloplasmin. Iron is released as Fe^{II} from ferritin, and the rate at which it is converted to circulating Fe^{III}_2-transferrin is dependent upon ceruloplasmin. This explains why Cu-deficient animals develop anaemia.

In addition, ceruloplasmin shows oxidase activity towards bifunctional aromatic amines and phenols, but with much higher K_m values, and also to a group of pseudosubstrates that can rapidly oxidize Fe^{II}. Ceruloplasmin may also have a role as a serum antioxidant.

62.1.8.5.2 Structural aspects of ceruloplasmin

There has been much uncertainty over the molecular weight and copper content. It appears to involve a single polypeptide chain of molecular weight about 130 000 with six or seven copper ions. On balance, there are two type 1, one type 2 and four type 3 copper centres. This is in accord with the fact that 44% of the total copper is paramagnetic and ESR-detectable.[977]

Similarities with respect to the location of cysteine, histidine and methionine residues in the proteins of azurin, plastocyanin and ceruloplasmin indicate that the type 1 centres in ceruloplasmin are similar to those in the other two proteins. The nine-line superhyperfine splitting in the ESR spectrum of the type 2 Cu has been interpreted in terms of four equivalent nitrogen ligands.[978] This was observed in a protein from which the type 1 copper was depleted by dialysis against ascorbate.

62.1.8.5.3 Mechanism of action of ceruloplasmin

The several functions of ceruloplasmin cannot be explained at present. It seems reasonable that this diversity is related to the activity of the copper centres. The general pattern of oxidase activity is probably similar to that of the other blue oxidases, with a type 3 binuclear site serving to bind and reduce dioxygen, with electrons transferred from the type 1 site. The type 2 copper may represent a substrate-binding site.

62.1.8.6 Copper and the Ethylene Effect in Plants

Ethylene plays an essential role in the development of plants, for example in germination, growth and fruit ripening. Carbons 3 and 4 of methionine appear to be the most important source of the gas *in vivo*, but the effect is also induced by externally applied gas. Acetylene and carbon monoxide are competitive with ethylene. This suggests that a metal ion is present at the ethylene receptor site, a view confirmed by the inhibition of alkene binding by dithiocarbamate.[979] The possibility that this metal is copper[980] is supported by the preparation of copper(I)–monoalkene complexes that show the tight binding of monoalkenes characteristic of the ethylene receptor sites of plants.[981]

62.1.9 THE BIOCHEMISTRY OF MOLYBDENUM

Molybdenum is the only transition element in the second row of the Periodic Table that is known to have a biological role. It is present in at least 15 enzymes, which are listed in Table 23,

Table 23 Molybdenum in Enzymes

Enzyme	*Source*	*MW*	*Mo*	*Other cofactors*
Xanthine oxidase	Bovine milk	300 000	2	$4Fe_2S_2$, 4FAD
Xanthine dehydrogenase	Animals, microbes	250 000	2	$4Fe_2S_2$, 4FAD
Aldehyde oxidase	Hog milk	270 000	2	$4Fe_2S_2$, 4FAD
Sulfite oxidase	Animals, *Thiobacillus novellus*	110 000	2	2 heme
Nitrate reductase (dissimilatory)	*Escherichia coli*	200 000	1	$4Fe_4S_4$
Nitrate reductase (assimilatory)	*Chlorella vulgaris*	360 000	4	4 heme, 4FAD
Formate dehydrogenase	*E. coli*		2-4	Fe_nS_n, heme, Se
Carbon monoxide oxidase	*Pseudomonas carboxydovorans*	300 000	2	$4Fe_2S_2$, 2FAD, Se
Nicotinic acid hydroxylase	*Clostridium barkerii*	300 000	2	Fe/S, FAD, Se
Chlorate reductase	*Proteus mirabilis*			
Biotin sulfoxide reductase				
Pyridoxal oxidase	*Drosophila* spp.		2	($4Fe_2S_2$, 4FAD)
Tryptophan side-chain oxygenase	*Pseudomonas* spp.			Heme
Nitrogenase	Range of microbes		2	Mo, Fe, S cluster, iron-sulfur cluster
Trimethylamine oxidase	*E. coli*			

and in several uncharacterized proteins. A number of the enzymes in Table 23 are hydroxylases. In many cases the substrate coordinates to the molybdenum, and electron transfer follows. This is in accord with the presence of other electron-transfer centres in the enzymes, which may be iron-sulfur, FAD or heme centres as noted in Table 23. A number of reviews are available.[982-991]

It is interesting to speculate on the chemical properties of molybdenum which make it suitable for its biological function. Obvious features in the chemistry of molybdenum are: (a) a range of oxidation states which can be stabilized in aqueous solution by the common ligands of biology; (b) the formation of oxo compounds and the sulfur analogue; (c) the ability to participate in atom-transfer reactions; and (d) the possibility of higher coordination numbers.

62.1.9.1 Molybdenum in Clusters — Copper Antagonism and Nitrogenase

One of the enzymes given in Table 23 is nitrogenase, which is responsible for the fixation of dinitrogen to give ammonia. Molybdenum probably serves as the binding site for N_2, and is present in the iron-molybdenum cofactor, which is a molybdenum-iron sulfide cluster. Nitrogenase will be considered in Section 63.1.14, which deals with the nitrogen cycle.

A second example of cluster formation involves the antagonism between molybdenum and copper. The presence of high concentrations of molybdenum in pasture soils is known to lead to symptoms of copper deficiency in animals. This has been attributed to the formation of thiomolybdates in the rumen of grazing animals, which then interfere with the metabolism of copper through the formation of cluster compounds of molybdenum and copper. It has been shown that thiomolybdate, MoS_4^{2-}, readily forms such clusters on reaction with phosphines and copper(II) salts under appropriate conditions. Structures are shown in Figure 38.[992,993] Reaction between thiomolybdate and copper compounds in aqueous solution have also been reported.[994]

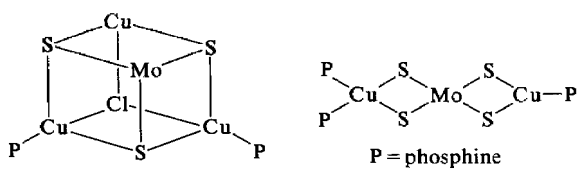


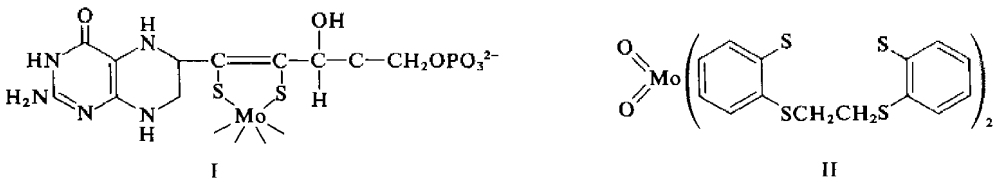
Figure 38 Some copper-molybdenum clusters

62.1.9.2 Molybdopterin — the Molybdenum Cofactor

The enzymes listed in Table 23 (with the exception of nitrogenase) appear to contain a molybdenum-binding cofactor.[995] These are interchangeable from enzyme to enzyme, where studied, and are probably identical. The factor is usually assayed by its ability to activate the

nitrate reductase from the *Neurospora crassa* mutant *nit-1*, which lacks the cofactor. This provides striking evidence in support of a common molybdenum cofactor in these enzymes.

The cofactor appears to include a novel pterin.[996-998] The properties of the pterin depend upon the nature of the side-chain in the 6-position. The structure shown in Figure 39 has been proposed[997] on the basis that molybdopterin is related to urothione, oxidized to pterin-6-carboxylic acid, and contains in the side-chain two sulfur groups, a double bond, a hydroxyl function and a terminal phosphate group. Two stable fluorescent derivatives of molybdopterin have been characterized,[999] which may be of value in view of the extreme instability of the native molybdoprotein when released from the enzyme.



I II

Figure 39 Molybdopterin and a possible model compound

The apocofactor is synthesized in the absence of molybdenum in *E. coli* and *N. crassa*. The cofactor from *E. coli* is soluble, but is isolated bound to a carrier protein from which it has to be separated.[998] Tungstate competes with molybdate for the molybdenum site in the cofactor, leading either to the formation of a demolybdo species or to an inactive form containing tungsten. The tungsten protein has been characterized in the case of sulfite oxidase,[1000] which, while inactive, is immunologically identical to the molybdenum cofactor.

Figure 39 shows a model ligand for the pterin. This provides an S_4O_2 environment for the molybdenum. In addition the species $Mo^{IV}OL$ and $Mo_2O_3(L)_2$ have been prepared.[1001]

62.1.9.3 ESR Spectra of Molybdenum Species

This technique has been of especial value in studying molybdoenzymes. Mo^{VI}, Mo^{V} and Mo^{IV} species have d^0, d^1 and d^2 configurations. Mo^{V} species are therefore ESR-detectable and are usually easily recognizable, with a slightly anisotropic set of g values in the region of $g = 1.96$–1.99. For ^{95}Mo and ^{97}Mo, $I = \frac{5}{2}$ but for other isotopes $I = 0$. The $I = \frac{5}{2}$ isotopes represent about 25% of natural molybdenum, and so the six-fold hyperfine splitting may be difficult to observe. Enrichment of the specimen in molybdenum isotopes with $I = \frac{5}{2}$ may be necessary. One complication may arise from coupling of the Mo^{V} centres, as is well known for dimeric complexes of Mo^{V}, with resulting loss of signal.

One important feature of Mo^{V} intermediate species during enzymatic reaction is the presence of superhyperfine splitting from a proton. Mo^{V} model compounds with coordinated N—H groups display superhyperfine coupling of the same order of magnitude as that found in molybdenum enzymes.[1002]

62.1.9.4 The Molybdenum Hydroxylases

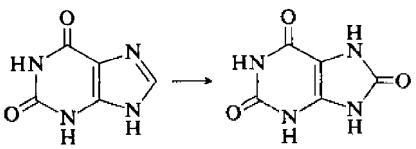
These enzymes catalyze the two-electron oxidation of purines, aldehydes and pyrimidines, sulfite, formate and nicotinic acid in the general reaction shown in equation (49). These enzymes show some differences in properties. Xanthine oxidase, xanthine dehydrogenase and aldehyde oxidase all have relatively low redox potentials and a unique 'cyanolyzable' sulfur atom, and so will be discussed together.

$$RH + H_2O \rightarrow ROH + 2H^+ + 2e^- \qquad (49)$$

62.1.9.4.1 Xanthine oxidase, xanthine dehydrogenase and aldehyde oxidase

Xanthine oxidase and xanthine dehydrogenase are two closely related enzymes which differ in the nature of their terminal electron acceptor, the oxidase using O_2 and the dehydrogenase using

NAD^+. They catalyze the hydroxylation of purines. Equation (50) shows the xanthine oxidase-catalyzed oxidation of xanthine to uric acid. Xanthine oxidase is probably the most well-studied molybdenum enzyme. There is good evidence that the molybdenum is the site for binding and reduction of xanthine. The enzyme contains Mo^{VI} in the resting form, while Mo^{IV} and Mo^{V} are implicated during catalysis.



(50)

Aldehyde oxidase catalyzes the oxidation of aldehydes to carboxylic acids by dioxygen, but also catalyzes the hydroxylation of pyrimidines. Despite its rather broad specificity for substrates, it may well be that aldehyde oxidase should be regarded primarily as a pyrimidine hydroxylase. Thus, xanthine oxidase and aldehyde oxidase catalyze the hydroxylation of purines and pyrimidines respectively. The oxygen incorporated into the product comes from water, not O_2. The dioxygen serves as the electron acceptor and other oxidizing agents may be used.

As normally isolated, xanthine oxidase is a mixture of the active enzyme and a catalytically inactive degradation product, namely the desulfo xanthine oxidase. The deactivation of the enzyme by added cyanide results from the abstraction of this sulfur atom to give thiocyanate. Loss of the sulfur atom to give desulfo xanthine oxidase results in marked changes in the ESR signals[1003] of the molybdenum(V), and in changes in the absorption spectra and redox potential of the molybdenum.[1004] Changes in these essential properties of the enzyme on loss of the sulfur atom have led to much interest in the identity of the group which loses the sulfur, and in possible structural and mechanistic implications. Early candidates for the source of the sulfur atom were cysteine[1005,1006] and persulfide.[1007] Molybdenum complexes with persulfido groups have been prepared,[1008,1009] and these will undergo sulfur abstraction reactions with cyanide.[1010] The present view is that an Mo=S group is involved.

Xanthine hydrogenase and aldehyde dehydrogenase also give desulfo proteins which have no catalytic activity and lower redox potentials. A molybdenum protein from *Desulfovibrio gigas* has been isolated, which appears to have similar properties to the desulfo proteins.[1011]

Desulfo enzymes can be regenerated by anaerobic treatment with sulfide plus dithionite. Cyanide-inactivated turkey liver xanthine dehydrogenase is also reactivated by selenide, suggesting that selenium may replace sulfur in the active centre.

Xanthine oxidase has a molecular weight of 300 000 and is dimeric. Each subunit contains one Mo, one FAD and one each of two types of Fe_2S_2 cluster. The Mo^{V} ESR signals are split by the iron-sulfur centre I, so allowing the calculation of distances between the two centres.[1012-1014] The most recent estimate is close to 15 Å, with a lower limit of 12 Å, a value that holds also for aldehyde oxidase.[1015]

X-ray absorption edge and EXAFS measurements are now available for a number of molybdenum enzymes, as shown in Table 24. The coordination environment around molybdenum in the desulfo xanthine oxidase involves two terminal oxo groups (Mo=O = 1.75 Å), two sulfur atoms at 2.5 Å and one at about 2.9 Å. In the active enzyme, a sulfur atom at about 2.25 Å (M=S) replaces one of the terminal oxygen atoms of the desulfo enzyme.[1016,1017] An independent study[1018] has given similar but not identical results for xanthine oxidase. Oxidized xanthine dehydrogenase appears to be similar to xanthine oxidase; oxidized desulfo xanthine dehydrogenase shows the loss of the M=S group and the formation of an additional M=O group.[1019] However, both desulfo and active xanthine dehydrogenase in the reduced form show one M=O group only.[1019]

These results support strongly the proposal[1020] that a terminal sulfur group is lost from the molybdenum on formation of the desulfo enzyme and replaced by a terminal oxo group. This will account for the difference in pK_a value observed for xanthine oxidase and the desulfo enzyme, which has been attributed to the protonation of the sulfur and oxygen atoms respectively (equations 51 and 52). Evidence for such protonation arises from the observation that the ESR spectrum of the Mo^{V} species shows ligand hyperfine splitting, which can be attributed to a proton. The doublets coalesce in D_2O showing that the proton is exchangeable,[1021] while the pH dependence of this phenomenon gives an apparent pK_a value of about 8. It appears, however, that the molybdenum(V) interacts with two protons during the catalytic reaction.[1021] Studies with 8-deuteroxanthine show that a proton from the 8-position in xanthine transfers to the enzyme, and is the proton more strongly coupled to the molybdenum. This proton could be transferred to the Mo=S group, as

Table 24 X-Ray Absorption Edge and EXAFS Data on Molybdenum Enzymes[a]

Enzyme	*Redox state*	*Donor atoms (bond length, Å)*	*Ref.*
Xanthine dehydrogenase	Oxidized	1O (1.70), 1S (2.15), 2S (2.47)	1
	Reduced	1O (1.68), 3S (2.38)	1
Desulfo xanthine dehydrogenase	Oxidized	2O (1.67), 2S (2.46)	1
	Reduced	1O (1.66), 2/3S (2.33)	1
Xanthine oxidase		1O (1.75), 1S (2.25), 2S (2.50), 1S (2.90)	2
Desulfo xanthine oxidase		2O (1.75), 2S (2.50), 1S (2.90)	2
Xanthine oxidase		1/2O (1.71), 2S (2.54), 1S (2.84)	3
Sulfite oxidase	Oxidized	2O (1.68), 2/3S (2.41)	1
	Reduced	1O (1.69), 3S (2.38)	1
Nitrate reductase (assimilatory, *C. vulgaris*)	Oxidized	2O (1.71), 2/3S (2.44)	4
	Reduced	1O (1.67), 3S (2.37)	4
Nitrate reductase (dissimilatory, *E. coli*)	Oxidized	O?	
	Reduced	1/2O/N (2.10), 2/3S (2.36), X(2.8)	4

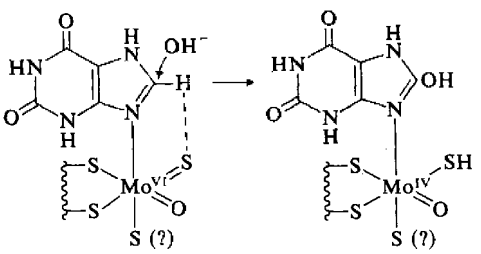
[a] There may be additional ligands not detected by these techniques.

1. S. P. Cramer, R. Wahl and K. V. Rajagopalan, *J. Am. Chem. Soc.*, 1981, **103**, 7721.
2. J. Bordas, R. C. Bray, C. D. Garner, S. Gutteridge and S. S. Hasnain, *Biochem. J.*, 1980, **191**, 499.
3. T. D. Tullius, D. M. Kurtz, S. D. Conradson and K. O. Hodgson, *J. Am. Chem. Soc.*, 1979, **101**, 2776.
4. S. P. Cramer, L. P. Solomonson, M. W. W. Adams and L. E. Mortenson, *J. Am. Chem. Soc.*, 1984, **106**, 1467.

shown in equation (53), which also suggests a possible coordination environment for the molybdenum.

$$E{-}Mo{=}S + H^+ \underset{pK_a = 8}{\rightleftharpoons} E{-}Mo{-}SH \qquad (51)$$

$$E{-}Mo{=}O + H^+ \underset{pK_a = 10}{\rightleftharpoons} E{-}Mo{-}OH \qquad (52)$$



(53)

Xanthine oxidase also has a site that will bind anions such as nitrate. This appears to be the substrate-binding site on molybdenum.

The action of subtilisin on xanthine dehydrogenase monomer gives a fragment of molecular weight 65 000, which contains the molybdenum and iron-sulfur centres, and from which the flavin is absent. This fragment will not catalyze xanthine-dependent reduction of NAD^+. The action of various proteases suggests that xanthine dehydrogenase is made up of three domains represented schematically in Figure 40.[1022]

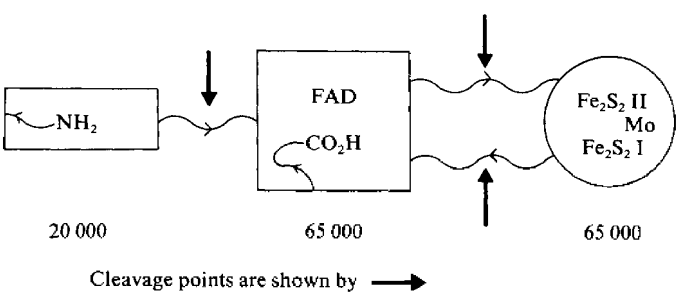
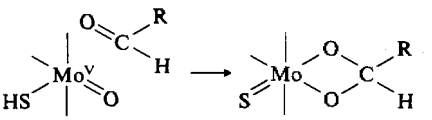


Figure 40 Proteolytic cleavage of xanthine dehydrogenase

The technique of ESR spectroscopy has been of especial value in the study of molybdenum-containing enzymes. Oxidized xanthine oxidase contains Mo^{VI} but a number of ESR signals due to Mo^{V} are developed under various reducing conditions.[991] These have been classified as 'very rapid' (for reduction with xanthine at high pH), 'rapid' (1 and 2) (for reduction with any substrate), 'inhibited' (for the enzyme treated with aldehydes), 'slow' (for the desulfo enzyme reduced for long time periods) and 'resting II' (a signal resistant to redox changes, found for the desulfo enzyme treated with ethylene glycol). Only the very rapid and rapid signals are observed during the turnover time of the enzyme and are therefore of catalytic relevance. The interaction with aldehydes gives an Mo^{V} signal attributed to the reaction product shown in equation (54). The conversion to this species is not stoichiometric, reflecting the distribution of molybdenum in the oxidation states (VI), (V) and (IV). It appears that there is also an Mo^{IV} aldehyde species, which is not in rapid equilibrium with the Mo^{V}-inhibited species.[1023]



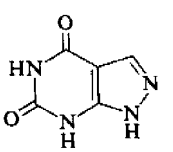
(54)

It is probable that during enzyme turnover, there is a two-electron abstraction from the substrate to give Mo^{IV} and of a proton by a molybdenum ligand; that is an effective abstraction of hydride. The two electrons will then be distributed amongst the reducible centres in the protein to extents appropriate to their relative redox potentials, prior to transfer to O_2 or other added oxidizing agent. There will be a transient reoxidation of Mo^{IV} to give the observed Mo^{V} species. The redox potentials for the molybdenum and other redox centres are known.[1024–1028] Those for molybdenum are given in Table 25. It may be seen that a wide range is covered for the various enzymes, showing the versatility of the molybdenum centre in enzymes.

Table 25 Redox Potentials (E_m, mV) of Molybdenum Centres in Enzymes

Enzyme	Mo^{VI}/Mo^{V}	Mo^{V}/Mo^{IV}
Xanthine oxidase	−373	−375
Xanthine dehydrogenase	−357	−397
Aldehyde oxidase	−359	−351
Desulfo xanthine oxidase	−354	−386
Desulfifo xanthine dehydrogenase	−397	−433
Mo protein from *D. gigas*	−415	−530
Sulfite oxidase	+38	−163
Nitrate reductase (*C. vulgaris*)	−34	−54
Nitrate reductase (*E. coli*)	+180	+220
Formate dehydrogenase	−330	−470

The evidence for the involvement of Mo^{IV} seems clear. Upon reduction of the enzyme with less than stoichiometric amounts of reagent or substrate, an ESR signal appears which is lost when further reductant is added. The tungsten-containing sulfite oxidase[1000] can be reduced to ESR-active W^{V} with dithionite, but the W^{V} signal is stable in the presence of additional reducing agent. It appears that the tungsten cannot be reduced to W^{IV}, so accounting for the inactivity of the enzyme. Excellent evidence for the importance of Mo^{IV} comes from studies with inhibitors. Allopurinol is a substrate for the enzyme, but its oxidation product alloxanthine (**9**) is strongly bound at the active site. Removal of excess reagents allow quantitative reoxidation with $[Fe(CN)_6]^{3-}$. After allowance for oxidation of the flavin and iron–sulfur centres, it may be shown that the molybdenum requires two electrons to be oxidized back to Mo^{VI}.[1029] Because of this property, allopurinol is used in the control of hyperuricemia in gout.[1030] More potent inhibitors are folate compounds and 2-amino-4-hydroxypteridine.[1031] 8-Bromoxanthine binds at the Mo centre and again seems to involve Mo^{IV}.[1032]



(**9**)

The very rapid and rapid signals are suggested to be due to species resulting from the breakdown of an intermediate at high and low pH values.[1033] The rapid signal shows the interaction of a proton at the active site. The types 1 and 2 rapid signals are thought to involve different coordination geometries around the molybdenum.

Any discussion of the mechanism of xanthine oxidase should attempt to incorporate the special features of xanthine oxidase (and xanthine dehydrogenase and aldehyde oxidase) which are not present, for example, in sulfite oxidase. There are two such features at least: (a) the involvement of two protons rather than the one found for sulfite oxidase, and (b) the presence of the cyanolyzable sulfur atom. The mechanistic features discussed so far involve the abstraction of two electrons and a proton. This means that a carbonium ion is generated, which could undergo attack by a nucleophile. Thus, the presence of a nucleophile at the active site could lead to the formation of a covalent intermediate that will break down to give the products.[1032] The nucleophile could either be the cyanolyzable sulfur atom or a group associated with the second proton. A possible scheme is shown in Figure 41.

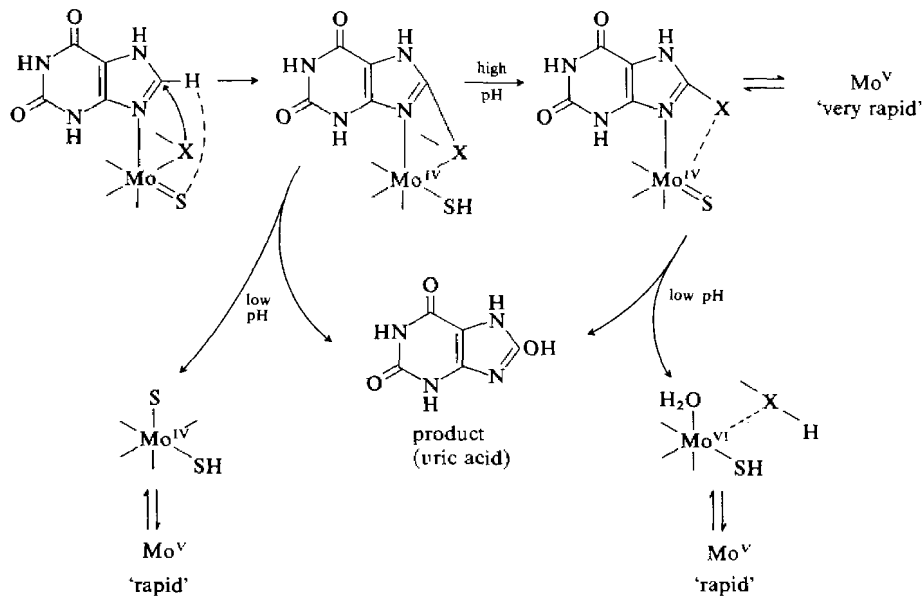


Figure 41 The mechanism of action of xanthine oxidase

62.1.9.4.2 Carbon monoxide oxidase, nicotinic acid hydroxylase, formate dehydrogenase and other hydroxylases

Nicotinic acid hydroxylase from *Clostridium barkerii* catalyzes reaction (55), the hydroxylation of a pyridine group, and has similarities to xanthine dehydrogenase. Nicotinic acid hydroxylase is a 300 000 molecular weight flavoprotein containing iron-sulfur and FAD centres, selenium[1034] and a molybdopterin cofactor.[1035] Formate dehydrogenase contains selenium as selenocysteine,[1036] but this does not appear to be the case for nicotinic acid hydroxylase. The possibility that the selenium is incorporated into the molybdopterin cannot be excluded at present.

$$\text{nicotinic acid} + H_2O + NADP^+ \rightleftharpoons \text{6-hydroxynicotinic acid} + NADPH + H^+ \quad (55)$$

Carbon monoxide serves as the sole carbon and energy source for the carboxydo bacteria under aerobic conditions. Using water as the oxygen donor, carbon monoxide oxidase catalyzes the hydroxylation of carbon monoxide, giving carbon dioxide or bicarbonate for assimilation. Most work has been carried out on the enzyme from *Pseudomonas carboxydovorans*.[1037,1038] The activity of carbon monoxide oxidase is considerably stimulated upon anaerobic treatment with sulfide and dithionite, or by aerobic treatment with selenite. The binding of selenite to the oxidase specifically activates the CO → methylene blue reaction.[1039] The molybdenum cofactor liberated from selenium-activated carbon monoxide oxidase does not contain selenium. Here, then, the

selenium may be present as a selenocysteine residue, in which case this would be expected to be the case also for nicotinic acid hydroxylase.

The biochemistry of the aerobic carbon monoxide-oxidizing bacteria is of considerable interest in that the respiratory chain is not sensitive to inhibition by CO, due, it is suggested, to the presence of a CO-insensitive *o*-type cytochrome functioning as a terminal oxidase.[1037]

Carbon monoxide oxidase is highly specific for CO and does not catalyze the hydroxylation of xanthine, pyrimidines or aldehydes. It has no nitrate reductase or sulfite oxidase activity. One unusual feature is that the active enzyme shows a stable Mo^V ESR signal in the absence of substrate or other reducing agent. The substrate, CO, did not affect the different ESR signals (from Mo or Fe/S centres) within the turnover time of the enzyme. The use of ^{13}CO showed no isotope effect upon the resting Mo^V signal of carbon monoxide oxidase, suggesting that CO is not bound directly or through oxygen bridges to the molybdenum.[1039a] At this stage it is not possible to speculate upon reaction mechanism.

Formate dehydrogenases have been isolated from aerobic and anaerobic bacteria, yeasts and plants, and comprise a rather heterogeneous group of enzymes. *E. coli* contains two forms of formate dehydrogenase which can be either soluble or membrane bound.[1040]

Two forms have been isolated from the methanogen *Methanococcus vannielii*, namely a 105 000 molecular weight protein containing molybdenum and an iron–sulfur centre, and a high molecular weight complex which contains selenium in addition.[1041] The formate dehydrogenase from *Methanobacterium formicicum*[1028] contains a molybdoprotein. Reduction of the enzyme generated ESR signals, confirmed to be due to molybdenum by the use of ^{95}Mo-enriched formate dehydrogenase and the observation of hyperfine splitting. A second component of the ESR spectrum showed no splitting, and was assigned to a reduced iron–sulfur centre. Cell culture in a medium containing high tungstate concentration gave an enzyme without activity or an ESR spectrum.

The Mo^V ESR signal is complicated by ligand hyperfine splitting due to two protons, a situation similar to that found for xanthine oxidase. A unique feature lies in the appearance of the ESR signals at $g_{av} > 2.0$. This may suggest that the molybdenum in this formate hydrogenase has a different coordination geometry from the octahedral or square pyramidal structures suggested by ESR data on other enzymes.[1042]

A molybdenum cofactor has been isolated from *Proteus mirabilis*[1043] and has a molecular weight greater than 1000. The molybdoenzymes of *E. coli*, in addition to the formate dehydrogenases described above and the nitrate reductase (Section 62.1.9.6), also include the membrane-bound trimethylamine oxidase[1044] and the soluble biotin sulfoxide reductase.[1045]

62.1.9.5 Sulfite Oxidase

Sulfite oxidase catalyzes the oxidation of sulfite to sulfate, with cytochrome *c* as the ultimate physiological electron acceptor. Sulfite is oxidized at the molybdenum site, which is in turn reoxidized by the heme.

The enzyme is a dimer, of molecular weight 55 000 per subunit. The molybdenum and heme centres seem to be in different domains, as shown by proteolysis.[1046–1048]

Sulfite oxidase (and nitrate reductase) has a higher redox potential for Mo than other molybdenum enzymes. Although both are inhibited by cyanide in their reduced states, this process is reversed by oxidation and thiocyanate is not released. There appears, therefore, to be no terminal S atom to be removed with cyanide. Conclusions from EXAFS measurements on sulfite oxidase are shown in Table 24.[1019] EXAFS data on *Chlorella* assimilatory nitrate reductase suggest it is similar to sulfite oxidase.[1049] The important feature in the EXAFS results for sulfite oxidase is that there is a loss of an oxo group in going from the oxidized to reduced form. This leads to a simple mechanism in which the molybdenum site acts as an oxo-transfer reagent, converting sulfite to sulfate. The Mo^{IV} generated in this way can then accept a new oxygen from water on being reoxidized to Mo^{VI}.

62.1.9.6 Assimilatory and Dissimilatory Nitrate Reductase

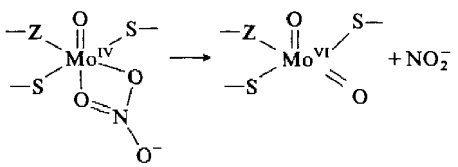
Nitrate reductases have been isolated from bacteria, plants and fungi and always contain molybdenum. Two types may be distinguished: (a) the assimilatory nitrate reductases which catalyze the reduction of nitrate to nitrite, which ultimately is reduced to ammonia and used by

the cell for growth, and (b) the dissimilatory nitrate reductases which use nitrate as a terminal electron acceptor in the absence of dioxygen. The structures of nitrate reductases vary considerably, and various electron-transfer centres are used. Thus the electron transfer pathway in the assimilatory nitrate reductase of *Neurospora crassa* is given in equation (56).

$$\text{NADPH} \rightarrow \text{FAD} \rightarrow \text{cyt } b_{557} \rightarrow \text{Mo} \rightarrow NO_3^- \tag{56}$$

Pseudomonas aeruginosa can synthesize both types of nitrate reductase, depending upon the environmental conditions, the dissimilatory enzyme being repressed by dioxygen.[1049]

Nitrate reductase from *Chlorella*, an assimilatory enzyme, is a homotetramer of molecular weight 360 000 and contains one each of Mo, heme and FAD per subunit. The nitrate reductase from *E. coli* is a dissimilatory enzyme. EXAFS data are available on the molybdenum sites in both enzymes (Table 24).[1050] The environment of the molybdenum in the assimilatory enzyme is similar to that found for sulfite oxidase, with at least two sulfur ligands near the molybdenum and a shuttle between monoxo and dioxo forms with redox change in the enzyme. This allows a similar mechanism to be put forward for the assimilatory nitrate reductase,[1051] shown in equation (57), where an oxo group is transferred from nitrate to Mo^{IV} with production of nitrite and Mo^{VI}.



(57)

The structure of the reduced dissimilatory reductase from *E. coli* shows noticeable differences. In particular, there is a long-range interaction with an unidentified neighbour. It is tempting to suggest that this is an iron atom from an iron–sulfur centre, and to propose that there is a concerted two-electron transfer to the nitrate.[1052] The different function of the two enzymes can then be related to the different mechanisms.

The assimilatory nitrate reductase from *Chlorella* contains the molybdenum cofactor, as evidenced by the ability of the enzyme to donate the cofactor to the nitrate reductase of the mutant *nit-1* of *N. crassa*. Reduction of the enzyme with NADH gives the Mo^V ESR signal, which is abolished on reoxidation with nitrate. Line shape and *g* values of the signal show a pH dependence similar to those observed previously for sulfite oxidase. The signal observed at pH 7.0 shows evidence for interaction with a single exchangeable proton.[1053]

ESR studies on the dissimilatory nitrate reductase are also available. Two signals arising from a high pH and a low pH species of Mo^V have been found in the enzyme from *E. coli*,[1054] the low pH species having a strongly coupled proton.[1055] Studies on the dissimilatory nitrate reductase from *Ps. aeruginosa*[1056] show evidence for three Mo^V species, a high pH species, and nitrate and nitrite complexes of a low pH species. The iron–sulfur clusters were classified as a [3Fe–4S] cluster in the oxidized enzyme (arising from degradation of a [4Fe–4S] core), and an unusual low potential $[4Fe–4S]^+$ cluster in the reduced enzyme. The nitrate complex with the nitrate reductase involves a strongly coupled proton, which is in accord with reduction of nitrate involving electron transfer and protonation.

62.1.9.7 Some General Comments on the Role of Molybdenum

The results described in the previous sections have demonstrated the versatility of molybdenum as a reaction centre in biology. The molybdenum cofactor stands at the centre of an important network of cellular functions that are all catalyzed by molybdoenzymes. The similarities and differences in these reactions are of great interest, and relate clearly to the detailed arrangement of terminal sulfur and oxygen atoms. However, the unexpected results found for carbon monoxide oxidase and the requirement for selenium in some cases indicate that other factors are also important.

An organism such as *E. coli* has at least five molybdoenzymes. It will be of great interest to look at the synthesis, availability and cellular distribution of the molybdenum cofactor and its relationship to the function of these molybdoenzymes at different stages of the cell cycle. The study of chlorate-resistant[1057] and nitrate reductase-deficient[1058] mutants of *E. coli*, which are

mutations involving molybdoenzymes, should throw light on the way in which synthesis and use of the molybdenum cofactors are controlled.

It is clear, then, that while significant advances have been made in the biochemistry of molybdenum, there is much that remains to be done before these processes can be understood at the molecular level.

62.1.10 VANADIUM, CHROMIUM AND OTHER ELEMENTS

Vanadium and chromium have been shown to be essential by nutritional studies. Of the remaining metals, it appears possible that tin and tungsten may be essential. The biological properties of the essential metalloids such as selenium[1059] and arsenic[1060] will not be considered.

62.1.10.1 Vanadium

Vanadium is widely distributed in the biosphere, and is present in mammalian tissues at concentrations of about 10 μmol dm^{-3} or less. Its role as an essential element was shown in the early 1970s when it was established that the growth of small animals was retarded when they were fed synthetic diets containing less than 10 p.p.b. vanadium. It is now recognized that vanadium has numerous physiological effects,[1062] although the nature of its essential physiological role is not known with certainty.[1063] Vanadium-containing nitrogenase and bromoperoxidase[1566] have been isolated.

62.1.10.1.1 Physiological effects of vanadate(V)—competition with phosphate

In many cases the physiological effects of vanadium are due to the close similarity between vanadate and phosphate. Vanadate seems to inhibit specifically those ATPases that form a covalent phosphoryl enzyme intermediate during the enzymatic reaction cycle. Such behaviour was first noted for the (Na^+, K^+)-ATPase of the sodium pump, as described in Section 62.1.2.2.2, and attributed[57] to the binding of $H_2VO_4^-$ to the site of enzyme phosphorylation. This led to the suggestion that the physiological role of vanadium lay in the moderation of these processes, and this naturally occurring inhibitor has been used extensively in the study of the mechanism of the sodium pump since then. Vanadate has been found to inhibit, for example, the plasma membrane ATPase of *Neurospora crassa*[1064] and *Saccharomyces cerevisiae*,[1065] which are related to the (Na^+, K^+)-ATPase, the proton-translocating ATPase of *Mycobacterium phlei*[1066] and the Ca^{2+}-ATPase of red cell membranes.[1067] Other examples are given in ref. 1062.

Acid and alkaline phosphatases with phosphorylated intermediates are inhibited by vanadate. This has been exploited in the study of the role of alkaline phosphatase in mineralization.[1069] Vanadate also inhibits the ATP-dependent degradation of proteins in reticulocytes.[1070]

Vanadate is taken up by *N. crassa* when the cells are phosphate limited and growing in higher pH values. It takes place by the phosphate transport system II, which has high affinity for phosphate. Phosphate is a competitive inhibitor of vanadate uptake.[1071] This confirms the competitive relationship between phosphate and vanadate.

62.1.10.1.2 Inhibition of enzymes by vanadyl ion

Vanadate is reduced in red cells to vanadyl ion by intracellular glutathione following uptake through a phosphate transport system.[1072,1073] Free vanadyl is normally unstable with respect to oxidation, but appears to be stable when complexed with intracellular proteins or smaller molecules.[1074] Vanadyl ion is a relatively powerful inhibitor of (Na^+, K^+)-ATPase. For pure fractions of the enzyme, inhibition was nearly complete at less than 5 μmol dm^{-3} vanadyl ion.[1075] The state of vanadyl ion at pH 7 is somewhat uncertain, but may involve a hydroxylated species. Vanadyl ion also inhibits alkaline phosphatase more effectively than does vanadate.[1076]

62.1.10.1.3 Vanadium as an insulin mimic

Vanadium appears to mimic the action of insulin. The incubation of rat adipocytes with 10–100 μmol dm^{-3} VO^{2+} or vanadate stimulates the transport of glucose and 2-deoxyglucose into

the cell[1077,1078] to an extent proportional to the vanadium content of the cells. The magnitude of this effect is equivalent to that produced by insulin. It appears that this may be due to VO^{2+}.[1077] Externally applied vanadyl ion is less effective than vanadate, possibly because the vanadate enters the cell more rapidly, and is then reduced to vanadyl ion which causes the insulin response.

The mode of action of the vanadyl ion in mimicking insulin is not clearly understood. It may function by regulating phosphatase activity in cells.

62.1.10.1.4 Accumulation of vanadium by sea squirts

The ascidians or tunicates (sea squirts) accumulate vanadium from seawater (about 5×10^{-8} mol dm^{-3}) to a level of about 1 mol dm^{-3} and store it in a dilute solution of sulfuric acid (pH < 2) in blood cells called vanadocytes. The tunicates thus concentrate vanadium several million-fold.[1079] NMR, ESR and EXAFS determinations on whole vanadocyte cells of *Ascidia ceratodes* and *Ascidia nigra* indicate that the vanadium is present mainly as aquated V^{III} probably complexed with sulfate. Some vanadyl ion (5–10%) is also present.[1080,1081]

A chromogen has been isolated from several species (tunichrome), but its role is not understood.[1082,1083]

It was once thought that the vanadium in vanadocytes acted as dioxygen carriers but this is now known to be incorrect. Many questions remain to be answered about the role of vanadium in vanadocytes.

62.1.10.1.5 Activation of enzymes by vanadium

While in general the biological activity of compounds of vanadium is directed towards the inhibition of enzymes, there are a few cases where vanadate activates enzymes. However, it is probable that this is an indirect effect resulting from the inhibition by vanadate of regulatory processes. This may be illustrated with reference to adenylate cyclase.[1084] Adenylate cyclase is regulated by a guanylnucleotide-binding protein. In the presence of GTP plus hormone this protein activates adenylate cyclase. Hydrolysis of GTP by an associated GTPase terminates the activation. Vanadate may thus cause activation of adenylate cyclase by inhibiting the GTPase. Decrease in the rate of hydrolysis of GTP at the regulatory protein will maintain adenylate cyclase in the active state. The recent discovery of a vanadium-containing nitrogenase is described in Section 62.1.14.

62.1.10.2 Chromium

Chromium was proposed as an essential element after the observation that rats fed with *Torula* yeast developed impaired glucose tolerance.[1085] The active ingredient in other yeasts was suggested to be a chromium complex, named the 'glucose-tolerance factor'. Brewers' yeast contains chromium in the range 0.35–5.4 $\mu g\ g^{-1}$.[1086]

There is now much interest in the biology of chromium,[1086–1088] which has been suggested to be involved not only in the action of insulin, but also in the activation of certain enzymes, and, possibly, the stabilization of nucleic acids. Chromium is also known to be carcinogenic and mutagenic at high concentrations, particularly as chromate. Chromate is reduced in rat liver microsomes to Cr^{III} and Cr^{V}. Cr^{V} is labile and may well be the carcinogenic form.[1089]

62.1.10.2.1 The glucose-tolerance factor[1090]

It has been proposed that GTF is related to a dinicotinatotris(amino acid)chromium(III) complex, which forms a ternary complex at the membrane receptor with insulin. Porcine insulin binds a $Cr(nic)_2$(glutathione) complex very tightly.

It has been suggested that GTF is not a chromium complex.[1091] This arises from the failure to isolate a biologically active Cr^{III} complex from extracts of brewers' yeast grown in a medium containing added Cr^{III}. Two fractions showed biological activity, but further purification resulted in the loss of chromium and the isolation of biologically active chromium-free compounds. One of these was largely tyramine (formed from tyrosine residues), but pure tyramine does not show GTF-type properties. The activity of this fraction must therefore be due to the minor component

(<10%) which could not be isolated. At this stage it appears probable that GTF is not a chromium complex, but it is possible that chromium may be involved in the *in vivo* synthesis of GTF, or that the active chromium complex has not been isolated.

62.1.10.3 Tungsten

As noted in Section 62.1.9, tungsten usually acts antagonistically against molybdenum. When tungsten is substituted for molybdate, particularly when administered with selenite, there is a substantial increase in formate dehydrogenase activity of *Clostridium thermoaceticum* cells and for *C. formicoaceticum*. Tungsten may be the preferred metal for formate dehydrogenase in these two cases. A tungsten-requiring, thermophilic methanogen has been reported.[1092]

62.1.11 THE TRANSPORT AND STORAGE OF TRANSITION METALS AND ZINC

The previous sections have indicated the essential role of these metals in living organisms. It is important, therefore, that transport processes are available for the uptake of these metals from the environment and their delivery to sites where they are incorporated into biological molecules. There may also be mechanisms for the storage of excess metal until it is required by the cell, and for the reprocessing of metals liberated by the breakdown of the molecules in which they are bound.

Transport and storage processes involving iron are by far the best understood, both for mammalian systems (transferrin and ferritin) and for microbes (the siderophores in iron transport). In addition, knowledge of the transport and storage of copper and zinc in mammalian systems is advancing steadily, although awareness of microbial transport systems in general is poor.

Mammalian control systems for iron transport are more complex than those found in microorganisms. In both cases, there is the problem that, at physiological pH values, iron will be present as highly insoluble Fe^{III} polymeric species of composition Fe(O)(OH). Organisms need to solubilize iron and to prevent the iron forming insoluble species during storage.

62.1.11.1 Transport and Storage of Iron in Mammalian Systems

In an adult human some 65% of the total iron is found in hemoglobin and myoglobin, and the bulk of the remainder is found in the storage proteins ferritin and hemosiderin. A small amount is utilized in iron enzymes at any one time. An account will be given of ferritin and the transport protein transferrin, prior to a general discussion of iron transport and storage.

62.1.11.1.1 Ferritin

This iron storage protein is widely distributed in many mammalian cells, and also in invertebrates, plants, fungi and a number of bacteria, where it is associated with a *b*-type cytochrome. There have been considerable advances recently in the understanding of its structure and physiological function.[1093-1098]

Apoferritin consists of a hollow, spherical shell of external diameter 125 Å, which provides an inner cavity of maximum diameter about 80 Å for the storage of iron.

Apoferritin is made up of 24 subunits, arranged in 432 symmetry (Figure 42). The structure has been studied by X-ray crystallography,[1098-1100] while amino acid sequences are known for horse[1101] and human spleen[1102] ferritins and for rat liver ferritin.[1103] The crystal structure shows the presence of two types of channel into the cavity, namely six hydrophobic channels along the three-fold symmetry axes and eight hydrophilic channels along the three-fold symmetry axes. These channels are no more than about 4 Å wide at their narrowest point, but the protein may have some flexibility and so allow the entry of larger ions. The crystal structure shows that the hydrophilic channel is blocked by two adventitious Cd^{2+} ions, one bound by three glutamates and the other by three aspartates.

The inner cavity is filled with small crystalline particles of composition $[Fe(O)(OH)]_8$-$[Fe(O)(OPO_3H_2)]$, which is 57% iron and contains up to about 4500 iron atoms per ferritin molecule. While the core stores iron as Fe^{III}, it is generally accepted that deposition and mobilization involve Fe^{II}. Apoferritin rapidly accumulates iron in a solution containing Fe^{II} and O_2, but Fe^{III}

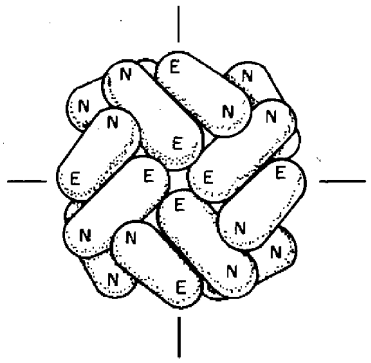


Figure 42 The structure of apoferritin. N = N-terminus; protein helices E form hydrophobic channels (reproduced with permission from *Adv. Inorg. Biochem.*, 1984, **5**, 39, Elsevier, Amsterdam)

is taken up slowly and to a smaller extent.[1104] The simplest view of this process is shown in equation (58), in which apoferritin catalyzes the oxidation of Fe^{II} with a ratio of four Fe^{II} per O_2, as found by some workers.[1105]

$$4Fe^{2+} + O_2 + 6H_2O \rightarrow 4Fe(O)(OH) + 8H^+ \quad (58)$$

The deposition of Fe^{II} into apoferritin using $^{18}O_2$ as the oxidant shows that only 3–4% of the oxygen atoms in the core were derived from O_2, irrespective of the amount of iron added. Use of $H_2{}^{18}O$ as solvent confirms that nearly all the oxygen atoms in the core were derived from the solvent. This work gave a stoichiometry of two Fe^{II} per O_2.[1106] It is known that this stoichiometry can vary from 2:1 to 4:1 under different conditions. In the case of the lower stoichiometry, superoxide or peroxide must be produced, although they have not been detected.

EXAFS measurements on the ferritin core and iron–glycine complex lead to a structure for the core in which the iron centres are surrounded by 6.4 ± 0.6 oxygens at 1.95 ± 0.02 Å distance in a distorted octahedral geometry. Each iron has 7 ± 1 iron neighbours at 3.29 ± 0.05 Å. These results, together with data on density and stoichiometry, lead to the structure shown in Figure 43. This involves a layer arrangement with iron in the interstices between two nearly close-packed layers of oxygen atoms, with only weak interaction between adjacent layers. The sheet is terminated by phosphate groups, appropriate for the stoichiometry, so that each strip will be about 60 Å in width and folded upon itself to fill the core.[1107]

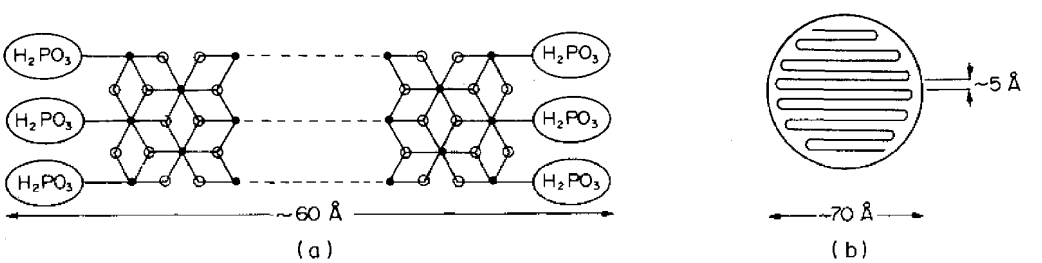


Figure 43 The structure of the iron-containing core in ferritin. (a) One way of using the phosphorus atoms to terminate the two-dimensional sheets into strips. From the stoichiometry there are nine Fe atoms per P, giving a width of ~60 Å. The length of the strip depends on the amount of iron in the micelle. (b) Schematic drawing of the folding of the strip into a 70 Å diameter micelle (reproduced with permission from *J. Am. Chem. Soc.*, 1979, **101**, 67, American Chemical Society, Washington, DC)

Ferritin has also been compared with iron–dextran by the EXAFS technique.[1108]

The apoferritin controls the deposition of the core. Reconstitution of ferritin under a range of conditions always gives the same structure, which is not the case in the absence of apoferritin. There are metal-binding sites on the protein shell. There is evidence for the binding of iron to apoferritin, probably by carboxyl groups, but there is little detailed information on these sites.[1098] On the other hand, other metal ions inhibit the formation of ferritin and may do this by binding at or close to the iron sites. Of most significance appear to be results on Tb^{3+}, Zn^{2+} and VO^{2+},

although several other metals have been studied.[1109,1110] ESR studies suggest that VO^{2+} binds at a stoichiometry of 0.5 VO^{2+} per subunit, indicating that the sites may involve ligands on two chains.[1111] Zn^{2+} has little effect on the binding of VO^{2+}, although it strongly inhibits ferritin formation, and so may bind at different sites. Crystallographic studies on the Zn^{2+}- and Tb^{3+}-substituted ferritin are in progress.[1098] Zn^{2+} and Tb^{3+} appear to bind with a stoichiometry of 24 cations per ferritin molecule.

The mechanism of deposition and mobilization of iron in ferritin has been much discussed.[1106,1112,1113] Ions and neutral molecules can all pass through the protein shell, due probably to the presence of entry channels of different character. The Cd^{2+} ions found in the hydrophilic channel in the crystal structure could be metal ions entering the shell.

Two proposals have been made for the mechanism of oxidation of apoferritin-bound Fe^{2+}. In the crystal growth model, the bulk of the Fe^{II} is oxidized to Fe(O)(OH) on the surface of the growing crystallite.[1104] It is initiated at catalytic sites on the interior surface of the protein. There is evidence that the mechanism of iron uptake by ferritin changes after the initial uptake. Initial uptake occurs more effectively with O_2 as the oxidizing agent, but in the latter stages O_2 and KIO_3 are equally effective.

The alternative view is that the protein is involved in catalysis of oxidation at all stages.[1113] It is suggested that two Fe^{II} ions bind at each of the pairs of metal sites found in the crystallographic studies, and that each pair interacts with dioxygen to give a μ-peroxo intermediate, (Fe—O—O—Fe), which then undergoes reaction to give Fe(O)(OH). The μ-peroxo pathway should lead to the incorporation of ^{18}O into the ferritin core, which was not observed.[1105] Nevertheless, the ^{18}O evidence is not unambiguous enough to rule out the protein catalysis model.

Iron may be released rapidly from ferritin *in vitro* by the action of reducing agents in the presence of iron chelators. Reducing agents are much more effective than chelators alone. The most effective reducing agent under physiological conditions appears to be reduced flavins, although the rate of reduction by dihydroflavins depends on many factors and seems to be controlled by the protein shell.[1097]

Apoferritin is synthesized in response to several factors, including the presence of iron. Added iron is taken up by the iron transport protein transferrin, which then binds to receptor sites on several types of cells which store iron.[1114,1115]

62.1.11.1.2 Transferrin

The transferrins are proteins that bind and transport iron as Fe^{III}.[1109,1116–1118] They include lactoferrin from milk, ovotransferrin from egg white, and serum transferrin from a range of organisms. Uteroferrin, considered in Section 62.1.5.5.2 on the purple acid phosphatases, is an iron-binding protein with phosphatase activity, that has been proposed to transport iron from maternal to foetal circulation.[824–826] There are distinct differences between the iron-binding sites in uteroferrin and transferrin, and so uteroferrin will not be discussed in this section.

Each of the transferrins is a glycoprotein of molecular weight about 80 000, made up of a single polypeptide divided into two similar domains. Both domains have a specific binding site for one iron(III) ion and an obligate anion which under physiological conditions will be carbonate. Iron is not bound in the absence of the anion. Other anions such as oxalate, malonate, citrate or EDTA will also activate the metal-binding site. The binding of Fe^{III} in the two domains of transferrin suggests that there is no interaction between them, in accord with distance measurements. A recent value is 35 Å, determined by consideration of fluorescence energy transfer between the two sites.[1119]

Amino acid sequences have been reported for human serum transferrin and ovotransferrin,[1120–1122] and partially for lactoferrin.[1123] The two halves show a high degree of homology.[1122] Partial proteolysis of transferrin gives half transferrins with one Fe^{III} site and molecular weights close to 40 000.[1124,1125] Thus, a fragment of molecular weight 35 600 has been obtained from human transferrin by proteolysis with thermolysin. This is derived from the N-terminal domain and is obtained by cleavage of a Pro—Val bond (residues 345 and 346).[1124] The two carbohydrate components of human serum transferrin are attached to residues 415 and 608 in the C-terminal domain of the protein, and appear to have little effect on the metal sites. Loss of the carbohydrate groups has no effect on the ESR spectra of the VO^{2+} complex of human transferrin.[1116]

The transferrins belong to the iron-tyrosinate group of proteins discussed in Section 62.1.5.5.2. Charge transfer from phenolate ligands to Fe^{III} accounts for the salmon-pink colour of transferrin. The detailed coordination environment of the iron in transferrin is not known with certainty, as

X-ray structural analysis has not yet been carried out at sufficient resolution. However, traditional chemical and spectroscopic methods have given a great deal of information. The involvement of tyrosine and histidine residues as ligands has been suggested by a comparison of potentiometric titration data for transferrin and the apoprotein, and by the use of chemical modification techniques and NMR and Raman spectroscopy. This has led to the conclusion that each iron is coordinated by two histidine and two or three tyrosine residues. The two homologous regions in the primary structure of transferrin which contain the metal-binding site only have two tyrosine residues each. The results of UV difference spectra have also suggested that there were two tyrosine ligands for each iron.[1126] The involvement of histidine as a ligand is supported by the observation of appropriate superhyperfine splitting in the ESR spectrum of copper transferrin. The coordination is completed by an aqua or hydroxo group and the obligate anion. The involvement of the anion as a ligand has been disputed but now seems established beyond question by spectroscopic studies on a range of metallotransferrins and various anions.[1127] The anion binds weakly to the apoprotein as a prerequisite for the binding of iron. It is reasonable that the anion binds to a positively charged group, which otherwise would hinder the binding of iron. The identity of the anion-binding group has been proposed to be a protonated imidazole of a histidine residue[1128] or a guanidinium group of an arginine residue.[1129] The former suggestion is supported by the fact that the conserved residues in both domains include three histidines. Two of these are ligands to iron, while the third could be the anion-binding site.

The iron centres in transferrin, in summary, are of approximately octahedral geometry with two tyrosinate, two imidazole, a carbonate (or bicarbonate) and a water molecule (or hydroxide ion) as ligands. This is consistent with the loss of three protons on binding of iron to apotransferrin, namely from two tyrosines and the aqua group. The ESR spectra of the two monoiron(III) half fragments differ slightly from each other, suggesting there are some differences between the two sites. The ESR spectrum is an unusual one which has not yet been reproduced in model compounds. A typical model[1130] for the iron site in transferrin is the complex of Fe^{III} with *N,N'*-ethylenebis(*o*-hydroxyphenyl)glycine. As hydrolysis of this compound occurs, so there is an increasing similarity in the zero-field splitting parameters in the ESR spectra of model and transferrin. These compounds appear to be six-coordinate.[1131,1132]

The significance of the two sites in transferrin has been much discussed. The sites are distinguishable spectroscopically and have different affinities for iron, which may be dependent on the anion used. The two sites release iron at different rates in a pH-dependent manner. The site in the C-terminal half of human serum transferrin (once designated the A site) retains its iron at pH 6.0 and so is the acid-stable site. The site on the N-terminal half is the acid-labile site.

It is now possible to separate the four principal species of transferrin [diiron(III), N-terminal monoiron(III), C-terminal monoiron(III) and the apotransferrin] by the techniques of polyacrylamide gel electrophoresis in the presence of urea.[1133] This allowed detailed studies of iron binding to transferrin, so that equations are now available for calculation of the distribution of iron between the various transferrin species.[1134]

The removal of iron from transferrin by ligands *in vitro* is difficult. Nevertheless, transferrin must be able to release iron readily when required. Reductive removal of iron does not occur, as the iron is released as iron(III). Studies on the delivery of iron to reticulocytes have failed to show that iron is taken up preferentially from either site in transferrin.[1135,1136] *In vitro* studies on the use of chelating agents to remove iron suggest that Fe^{III} transferrin undergoes a conformational change to give an open conformation. This species can form a complex with the chelating agent, which is eventually released as a complex with the Fe^{III}.[1137] Such a process could occur *in vivo*. Pyrophosphate mediates the removal of iron from transferrin to isolated respiring rat liver mitochondria. It appears that phosphates may be chelators of iron in removal of iron from transferrin in cells.

Lactoferrin occurs in high concentrations in human milk. It has high affinity for iron, and it may have a bacteriostatic function in depriving microbes of essential iron required for their growth. It supplies iron to intestinal tissue and probably has a nutritional role in supplying iron to newly born infants.

62.1.11.1.3 Phosvitin

Phosvitin is a highly phosphorylated, iron-containing protein found in egg yolk and serves as an important source of dietary iron.[1138] It could be viewed as a source of phosphate, as the protein contains about 130 residues of phosphoserine which appear to serve as ligand groups for iron.

It is also possible that this phosphoprotein could be involved in the transport of other metals.[1138]

Isolated phosvitin usually has two to three atoms of iron, with Fe/phosphate ratio about 1:50. Considerably larger amounts of Ca^{2+} and Mg^{2+} are bound [$(Ca^{2+}+Mg^{2+})$/phosphate ≈ 0.7]. It appears to have no known enzymatic or regulatory role.

62.1.11.1.4 The transport of iron

Iron entering the bloodstream from the gastrointestinal tract is thought to be present as Fe^{II}, and must be oxidized to Fe^{III} before binding to transferrin, which then delivers iron to many different types of cell. The non-enzymic route for oxidation of Fe^{II} in serum appears to be too slow for the formation of iron(III) transferrin. As noted in Section 62.1.8.5.1, the copper protein ceruloplasmin[905,975] has ferroxidase activity, being responsible for the oxidation of Fe^{II} to Fe^{III}. It is well known that deficiency of copper influences iron metabolism in animals, in accord with this role for ceruloplasmin.

Transferrin also has to cope with the iron liberated on breakdown of iron enzymes. It carries iron from the breakdown sites of hemoglobin in the reticuloendothelial cells of spleen and liver back to the sites in bone marrow for the synthesis of hemoglobin. Serum transferrin accounts for about 4 mg of body iron in humans, but delivers some 40 mg of iron daily to the bone marrow.

Serum transferrin is normally only about 30% saturated with iron. This explains why it has a relatively high capacity for binding other metals and so is implicated in the transport of ^{67}Ga,[1139] which is used as an imaging agent for various soft tissue tumours and inflammatory abscesses.[1140] Transferrin also facilitates movement of gallium across tumour cell membranes.[1141]

The uptake of iron from transferrin into cells has been best studied for reticulocytes, where there is heavy demand for iron for the synthesis of heme. Reticulocytes and, by analogy, other mammalian cells have receptor molecules on their plasma surface which bind transferrin. Characterization of the transferrin receptor from rabbit reticulocytes suggests that it is probably a glycoprotein of molecular weight around 200 000. The number of receptor sites in cells varies in response to the conditions. For example, treatment of K562 cells with the efficient iron chelator desferrioxamine results in an increase in the total number of receptors for transferrin.[1142]

It appears that both halves of the transferrin molecule contain a recognition site for the receptor, and that both are necessary for binding. Thus, the two halves of ovotransferrin are much less effective than the whole molecule in binding to the receptor and donating iron into the chick embryo red blood cell.[1143] One fragment of serum transferrin is ineffective.[1124]

The uptake of iron into the cell could follow several pathways. The iron could be released from the transferrin at the receptor site and be carried into the cell. Alternatively, the whole transferrin–receptor complex could be taken into the cell *via* endocytosis, and passed into an acidic compartment, where the iron is released, passed out of the compartment, and stored in ferritin.

The final step in the biosynthesis of heme takes place within the inner membrane of the mitochondria where the ferrochelatase catalyzes the insertion of Fe^{II} into protoporphyrin IX. Thus, the major part of the iron entering the cell is used in the mitochondria. Little is known about the way in which the iron enters the mitochondria. It seems unlikely that transferrin could deliver iron directly to mitochondria. Probably it is transferred to ferritin, which can then transfer it to the mitochondria. The mitochondria reduce exogenous flavin, which in turn reduces iron in ferritin,[1144] causing its release prior to uptake. Experiments suggest that the ferrochelatase reaction is the rate-limiting step in the biosynthesis of heme, and that the rate of mobilization of iron from ferritin by mitochondria with intact energy coupling and energy conservation properties is about three times the rate of formation of protoheme.

62.1.11.2 Transport and Storage of Other Transition Metals and Zinc in Mammalian Systems

Most of the transition elements can form complexes with transferrin and other proteins in serum, and can be stored in ferritin. This accounts for the effect of iron metabolism when the concentrations of these metals rise. Limited information which shows the presence of specific transport and storage systems is available on some metals.

62.1.11.2.1 Transport of copper

Copper is bound by albumin or histidine after uptake in the gut, and transported in this form to the liver, where it is transferred to ceruloplasmin. Some 95% of copper in human serum is

bound to ceruloplasmin, while the remainder is bound to albumin or histidine. It appears, therefore, that ceruloplasmin is the major transporter of copper,[975] although definitive confirmation is not available. It is reasonable to assume the existence of receptor sites in the various target tissues, and the possibility of copper release by a reductive method. If this occurs at the cell membrane then there may be an intracellular receptor for Cu^{I}.

62.1.11.2.2 Transport of zinc

About one third of the zinc in venous plasma is bound to α_2-macroglobulin, and the remainder to albumin, with the exception of trace amounts bound to histidine and cysteine.[1145] However, transferrin has been implicated in the uptake of zinc from the intestinal membrane, while albumin is involved in the removal of zinc from intestinal mucosal cells and its transport to the liver. Other ligands proposed for various transport processes for zinc are citric acid and picolinic acid.[1146]

62.1.11.2.3 Transport of nickel, manganese, cobalt and vanadium

Very little is known about the transport of nickel, manganese and cobalt. Plasma transferrin, conalbumin and citrate have been suggested to serve as carrier ligands. Transferrin is the main transport protein for vanadium in humans, and will transfer vanadium to ferritin.

62.1.11.2.4 Storage of copper and zinc. The role of metallothionein

The addition of copper, zinc, cadmium or mercury to animals results in the synthesis of a cysteine-rich protein called metallothionein.[1147–1149] These proteins have been isolated from a number of sources, and have molecular weights in the range 6000 to 12 000 with a cysteine content of about 30–35% of the total amino acid content. They have also been found in microorganisms and plants. These proteins are thought to play an important role in the storage of zinc and copper, and as a result of their storage capacity, are able to bind and detoxify cadmium and mercury.

Foetal and neonatal livers contain exceptionally high levels of copper compared to the adult organ. Thus, the livers of new-born rats contain as much as 20 times the level of copper and zinc metallothionein as that found in 70-day-old rats.[1150] Again, a metallothionein from foetal bovine liver contained eight copper and two zinc atoms per molecule of protein.[1151] These proteins can only be isolated with difficulty under oxygen-free conditions. It appears then that large amounts of copper (and zinc) are stored in the liver bound to metallothionein, and are mobilized as required for enzyme synthesis after birth.

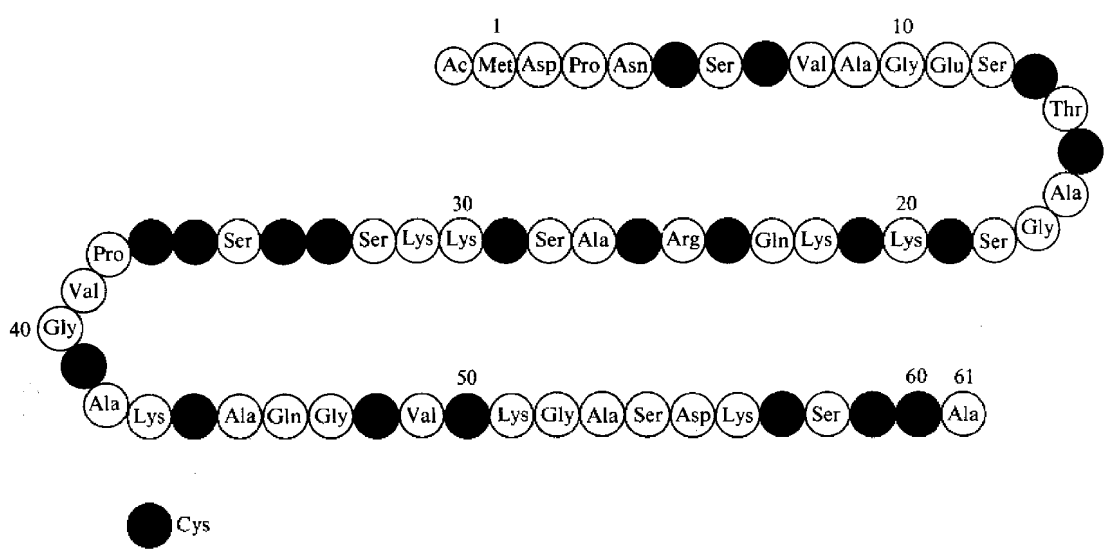


Figure 44 The amino acid sequence in equine metallothionein

The amino acid sequences of many mammalian metallothioneins are known.[1152] They all contain 61 residues with the cysteine residues distributed along the full length of the polypeptide chain, and with *N*-acetylmethionine and alanine at the N- and C-termini, respectively. All 20 cysteine residues are involved in the binding of up to seven metal ions *via* thiolate linkages. A typical amino acid sequence is shown in Figure 44.

The involvement of thiolate groups as ligands was first demonstrated by a comparison of the charge-transfer bands in metallothionein with those of thiolate complexes of zinc and cadmium. Tetrahedral environments around the metal were confirmed from a study of the *d–d* spectra of the cobalt-substituted protein,[1153] although the use of perturbed angular correlation spectroscopy of γ-rays suggests the presence of two types of environment.[1154] EXAFS measurements on Zn_5Cu_2 sheep metallothionein suggest a tetrahedral environment of four sulfur atoms with a Zn—S distance of about 2.29 Å.[1155]

Tetrathiolate coordination of the metals in metallothionein implies that the metals must be present in clusters with some of the cysteine residues serving as bridging ligands. The classification of the thiolate groups as bridging or terminal is confirmed by ESCA spectroscopy.[1156] The existence of clusters is in accord with ^{113}Cd NMR spectra of ^{113}Cd-labelled metallothioneins, which show ^{113}Cd–^{113}Cd spin coupling.[1157,1158] Decoupling experiments allow the suggestion of two metal-thiolate clusters containing four and three metals termed A and B respectively.[1157] The A cluster is formed by the C-terminal half of the protein and contains four metal ions bound to 11 cysteine residues, five of which are bridging. The B cluster binds three metal ions through nine cysteines, three of which are bridging.

The two clusters differ in their metal-binding properties. Mammalian Cd, Zn metallothionein contains four Cd ions in cluster A and two Cd ions and one Zn ion in cluster B.[1157,1159] Calf liver metallothionein contains three Cu ions in cluster B with Cd-displaceable zinc ions in cluster A.[1160] Studies on the binding of zinc and cadmium to human liver metallothionein show that binding occurs first in cooperative fashion to cluster A, followed by cooperative binding to cluster B. Incubation of the 7Cd metallothionein resulted in loss of Cd ions from cluster B initially.[1161]

The addition of Co^{II} to rabbit liver metallothionein appears to take place through the selective build-up of clusters, as shown by ESR, magnetic susceptibility and electronic spectroscopy.[1162] On filling up the metal sites on the apoprotein, the ESR signal from the high-spin Co^{II} increases in proportion to the binding of four metal ions, but declines on incorporation of the remaining three. The stepwise incorporation of Cd^{2+} into the apoprotein has been followed by electronic, CD and MCD spectra.[1149] In these studies it is suggested that, for both Co^{2+} and Cd^{2+}, the first four metal ions bind mainly to four thiolate groups each, and that cluster formation does not take place until the binding of the last three metal ions, where bridging thiolates become necessary as ligands. These two views of the binding of metals to metallothionein require some reconciliation and a decision on whether the first four metals form a cluster before further metal is bound. The magnetic data suggest that they do not.

Several studies on models have been reported, both on the binding of a range of metals to apometallothionein and the design of ligands, particularly with Cys-X-Cys and Cys-X-Y-Cys arrangements as found for metallothionein.[1163,1164] All metal derivatives appear to bind in metal-thiolate clusters.[1149] Platinum has also been found bound to metallothionein in rat tissues following treatment with cisplatin and the *trans* isomer.[1165]

Metallothioneins play an important role in the metabolism of copper, both in absorption and handling by the liver. Dietary supplementation with copper leads to a large increase in liver copper-metallothionein. The biological life of metallothionein can vary considerably. The half-life of Cu-metallothionein in zinc-deficient rats (12.3 h) was lower than that in zinc-sufficient rats (16.9 h).[1166] Usually zinc is found in Cu-metallothionein, so zinc may stabilize the copper metallothionein.[1167]

Metallothioneins probably participate in other cellular functions, for example in nucleic acid metabolism.[1168]

62.1.11.3 Transport of Iron in Microorganisms

Microorganisms, with the exception of certain of the lactobacilli,[1169] require iron, and have efficient mechanisms for its controlled uptake. Many organisms have several transport systems for iron. These have different affinities for iron, but those of high affinity are of especial interest. The extreme insolubility of iron in aerobic environments at physiological pH values presents a remarkable challenge to the microorganism. Furthermore, microorganisms living within higher

organisms have to compete for iron with animal transferrins which themselves have high affinity for iron. Pathogenic microorganisms have to scavenge iron *in situ*, for example, and so the availability of iron is closely linked to infections such as coliform invasions, septicaemia, gangrene, *etc.* All of this emphasizes the need for microorganisms to have highly efficient means for gaining iron.

Microorganisms accomplish this by synthesizing special ligands, the siderophores, which are low molecular weight compounds of remarkable affinity for Fe^{III}, having log K values greater than 30 and sometimes over 50. These ligands are synthesized in the cell in response to low levels of iron, and are then secreted. They bind and solubilize Fe^{III} to give siderophore–iron complexes, which are taken back into the cell *via* specific receptor sites on the cell surface.

Siderophores are synthesized by a range of organisms and a good many have now been characterized. Table 26 lists some of these. They may be isolated quite easily in many cases by growing organisms under low iron or iron-deficient conditions, when their syntheses are derepressed. The iron has to be removed selectively from the growth medium. This may be accomplished by the use of ion exchange resins such as Chelex-100, or immobilized 8-hydroxyquinoline,[1170] although a variety of methods have been used in the past.[1171] Growth of a number of organisms under such iron-limited conditions will lead to secretion of the siderophore into the culture medium. In some cases this will be shown by the accumulation of coloured degradation products of the siderophore in the culture supernatants. Procedures for isolation of the siderophores either as the Fe^{III} complex or as the iron-free form have been described.[1170]

Table 26 Classes of Siderophores

Type	*Example*	*Source*	*log K*
Cyclic tricatecholates	Enterobactin	Enteric bacteria	52
Linear catecholates	Agrobactin	*Agrobacterium tumefaciens*	
	Parabactin	*Paracoccus denitrificans*	
	Vibriobactin	*Vibrio cholerae*	
Cyclic trihydroxamates	Ferrichrome	Fungi (used by bacteria)	
Cyclic/linear hydroxamates	Fusarinines	Various fungi	
	Rhodotorulic acid	*Rhodotorula* spp.	31.2
	Neurosporin	*Neurospora crassa*	
	Ferrioxamine	*Streptomyces* spp.	30.6
Hydroxamate/citrate	Schizokinen	Bacilli	22.9
	Arthrobactin	*Arthrobacter* spp.	
	Aerobactin	*Salmonella* spp.	
Dihydroxamate/phenolate	Mycobactins	Mycobacteria	
Hydroxamate/catecholate/hydroxy acid	Pseudobactin	*Pseudomonas* spp.	
	Exochelin	Mycobacteria	

The siderophores fall into two main chemical types, with either catecholate-phenolate or hydroxamate donor groups. Several subdivisions of the hydroxamate siderophores are known, and additional examples continue to be identified. The siderophores, with a small number of possible exceptions, bind Fe^{III} with six hard, often negatively charged oxygen donor atoms. The exceptions may provide five such donor atoms and one nitrogen donor. These are groups well known to be good ligands for Fe^{III}. The siderophores bind Fe^{II} and other metal ions to a much lesser extent. Cr^{III} siderophores have been used as kinetically inert compounds, while Ga^{III} forms stable complexes, as does Al^{III} to a lesser extent.

The presence of siderophores in a medium may be shown by adding an iron(III) salt, as complex formation will be demonstrated by the colour of the Fe^{III}–siderophore complex, due to charge-transfer bands in the visible region. Chemical and spectroscopic tests allow ready classification into catecholate and hydroxamate types, for example the use of the Arnow and Czaky colorimetric reactions, respectively.[1172]

The siderophores have been discussed in Chapter 22 (Volume 2) and so will only be considered briefly here. All aspects of iron transport in microorganisms and clinical uses of siderophores have been reviewed on many occasions.[1169,1170,1172–1178]

62.1.11.3.1 Multiple pathways for iron transport

Many microorganisms have several pathways for uptake of iron, which are induced under particular conditions. This ensures that there is a continuous supply of iron at the correct concentration level. A low affinity system, which only functions in iron-sufficient conditions, seems to be widely distributed. This may involve the adsorption of Fe(O)(OH) polymer on the cell wall and transport of iron into the cell.

Escherichia coli has at least five independent transport systems, one of which is the low affinity pathway described above. In addition, it synthesizes enterobactin as a siderophore; it can take up the iron(III) complex of ferrichrome, a siderophore synthesized by certain fungi; there is a citrate-induced system, and a less common process involving aerobactin.

While *E. coli* only synthesizes one siderophore, other organisms synthesize a range of siderophores. Thus, the mycobacteria produce several classes of the siderophore exochelin, which differ in the solubility of the iron(III) complex.[1179] *Mycobacterium smegmatis* may produce up to eight exochelins.[1180] The structures of these exochelins are not known, but appear to be peptides with molecular weights less than 1000. Mycobacteria also synthesize mycobactins, which are intracellular iron-binding compounds, but which appear to be involved in iron transport in the early stages of growth. Under other conditions, mycobactins may serve as a store of iron. Mycobacteria also secrete salicylic acid and 6-methylsalicylic acid.

Shigella flexneri synthesizes the hydroxamate siderophore aerobactin (and a single outer membrane protein), but certain strains also synthesize enterobactin, a phenolate siderophore, in which case three additional outer membrane proteins are synthesized, similar to those produced by *E. coli* K-12 strains.[1181]

62.1.11.3.2 The catecholate siderophores

The best known example is enterobactin (otherwise called enterochelin), which is produced apparently by all enteric bacteria. It has three 2,3-dihydroxybenzoyl groups attached to a macrocyclic lactone derived from three residues of L-serine condensed head-to-tail. The structures of enterobactin and its iron complex are shown in Figure 45, which shows that the iron is bound by six phenolate oxygen atoms in an octahedral environment. Enterobactin has the highest known affinity for Fe^{III}, with log $K = 52$ at pH 7.4.[1182] The iron(III) complex can exist as isomeric forms, which may be associated with selectivity in binding to the receptor site.

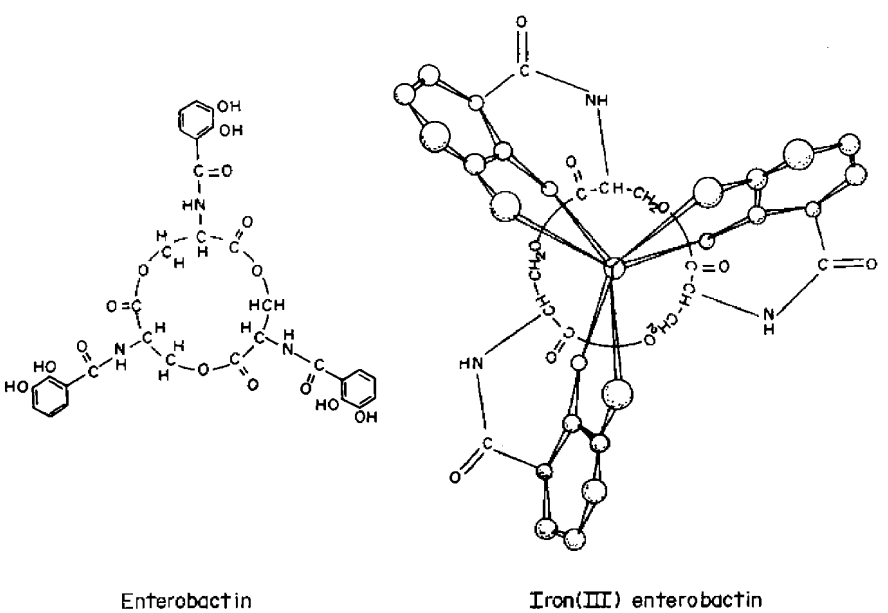
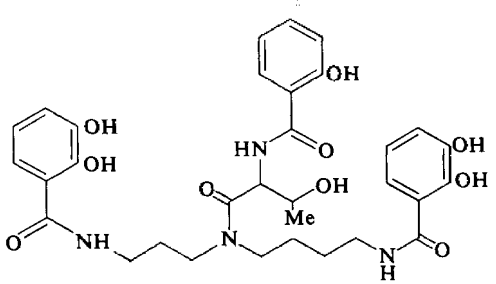
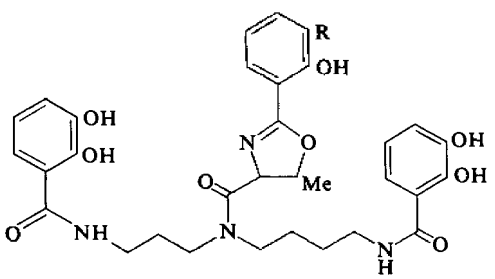


Figure 45 Enterobactin and its Fe^{III} complex

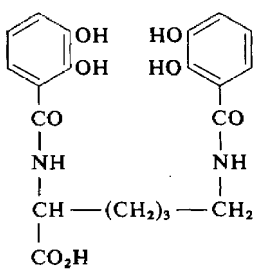
Linear catecholate siderophores are also known. The structures of parabactin and agrobactin are shown in Figure 46. They contain an oxazoline ring, which is subject to acid hydrolysis. The open-ring derivatives are agrobactin A and parabactin A. In these siderophores there is the possibility of coordination of the ring N atom, although agrobactin can provide six phenolate groups. The conformations of parabactin and its Ga^{III} complex have been examined[1183] by high resolution NMR. While the ligand exists in three separate conformers, only the Λ *cis* chelate was formed in the complex. This may be of significance as a recognition feature. A related example is vibriobactin, from *Vibrio cholera*, which contains three 2,3-dihydroxybenzoic acid functions, like agrobactin, but has two oxazoline rings.[1184]

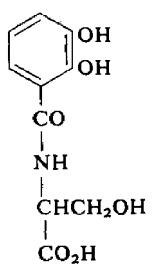


Parabactin A

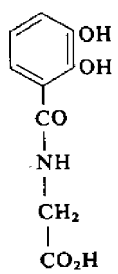


R = H Parabactin
R = Me Agrobactin





2,3-Dihydroxy-benzoylserine



Itoic acid

Figure 46 Parabactin, agrobactin and some small siderophoric phenolates

A number of catechols of lower molecular weight, which have siderophoric properties, have been isolated. Examples are shown in Figure 46. All organisms synthesizing enterobactin also form 2,3-dihydroxybenzoylserine, while a number of related species are also present. One of these, itoic acid, from *Bacillus subtilis* was the first phenolate siderophoric ligand to be isolated.[1185]

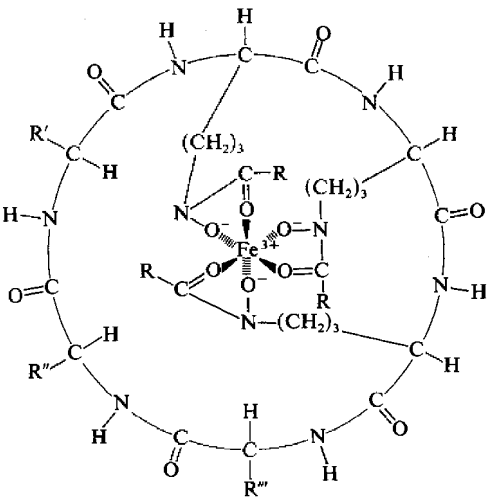
A great deal of work has been carried out on model compounds with phenolate and catecholate ligands,[1186,1187] and to some extent with modified siderophores.[1188] The important question of the mechanism of release of iron(III) from the siderophore has also been a central issue in these model studies.

62.1.11.3.3 The hydroxamate siderophores

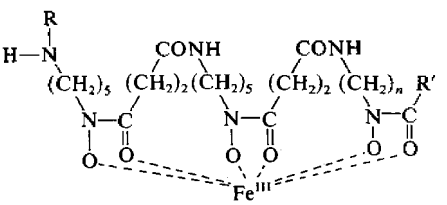
Ferrichrome was the first ligand of this type to be isolated (Figure 47). Ferrichrome is a cyclic peptide with three hydroxamic acid side-chains. It gives a neutral complex with Fe^{III}. A number of variations having substituents on the hexapeptide or on the acyl group are also found. The ferrichromes are synthesized by fungi, but they are also used by many bacteria as a source of iron, even though they do not synthesize the siderophore themselves.

The fundamental structural unit of the ferrichromes, N^{δ}-hydroxyornithine, is also present in rhodotorulic acid (and related compounds), the fusarinines (N^{δ}-acyl-N^{δ}-hydroxyornithine) and in neurosporin. The diversity of structure and biological activity of these siderophores results from the various substituents present in the peptide and acyl groups. The hydroxamate siderophores are better characterized from a structural viewpoint. X-ray diffraction data are available for the

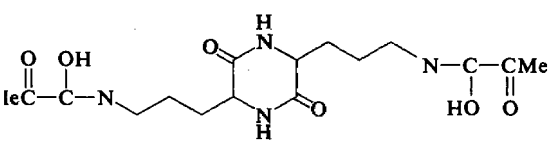
Fe^{III} complexes of ferrichrome,[1189] ferrichrome A,[1190] ferrichrysin[1191] and ferricrocin.[1192] These ferrichromes all show similar conformations of the peptide backbone and similar stereochemistry. Together with two fusarinine siderophores,[1193,1194] they all contain ornithine in the L configuration. Surprisingly the D isomer of N^{δ}-hydroxyornithine is present in neurosporin.[1195]



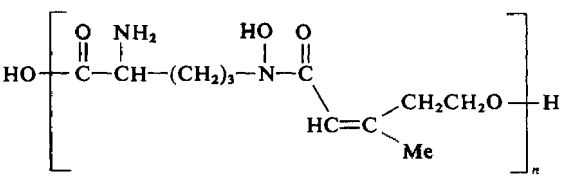
Ferrichromes



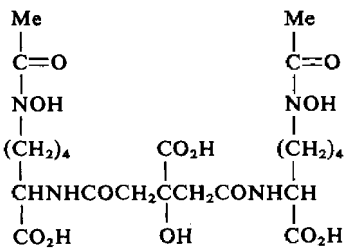
Ferrioxamines



Rhodotorulic acid

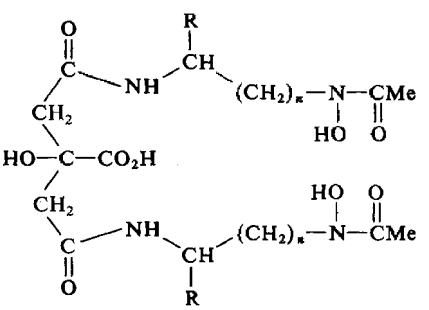


Fusarinines



Aerobactin

Figure 47 Ferrichrome and other hydroxamate siderophores



Schizokinen: R = H, $n = 2$
Aerobactin: R = CO_2H, $n = 4$
Arthrobactin: R = H, $n = 4$

Figure 48 The citrate hydroxamates

The ferrioxamines are a family of linear and cyclic siderophores built up from 1-amino-5-(hydroxyamino)alkanes and succinic and acetic acids. Figure 47 shows ferrioxamine B, a linear trihydroxamic acid, which is probably the best-known example. The mesylate salt of the deferri form of ferrioxamine B is used in the clinical treatment of iron-overloaded patients.

Exchange of iron between ferrioxamine B and ferrichrome A at pH 7.4 has a half-life of about 220 h.[1196]

Siderophores with citrate-hydroxamate structures (schizokinen, arthrobactin and aerobactin) are synthesized by enteric bacilli and *Arthrobacter* spp. Their structures are shown in Figure 48.

62.1.11.3.4 Pseudobactin

The pseudomonads produce a variety of siderophores, including pyochelin (a phenolic compound from *Pseudomonas aeruginosa*), the trihydroxamate nocardamine from *Ps. stutzeri* and pseudobactin from *Ps. fluorescens*. Pseudobactin is an unusual siderophore in that it carries the three functional groups found generally in siderophores, namely hydroxamic acid, catechol and α-hydroxyacid, which are substituents on a linear hexapeptide, as shown in Figure 49.[1197]

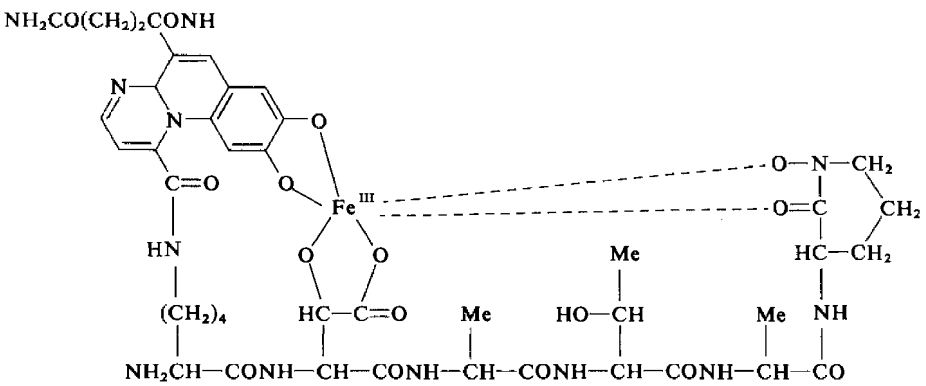


Figure 49 Schematic structure of pseudobactin

62.1.11.3.5 The binding of Fe^{III}–siderophore complexes to receptors and the release of iron into the cytoplasm

The iron–siderophore complex is too large to permeate the water-filled channels in the outer membranes of Gram-negative bacteria. Accordingly, a transport mechanism is necessary, involving proteins and expenditure of energy, although these are not well understood at present. The first stage in transport involves the recognition of the iron(III)–siderophore by receptor proteins in the cell membranes. These proteins are synthesized at low levels of iron. The receptor sites have been identified, partly because they also bind phages and antibiotics (which results in the death of the cell). Specific receptor proteins have been detected in *E. coli* K12 for the binding of iron(III) complexes of enterobactin, citrate, ferrichrome and aerobactin, although other proteins may also be necessary.

The receptor for Fe^{III}–enterobactin retains its affinity for the complex and for colicin B *in vitro* after extraction. The receptor has a dissociation constant of about 10 nmol dm^{-3} for Fe^{III}–enterobactin. The gene for synthesis of the receptor is *FepA*.

A range of modified enterobactin molecules have been synthesized in which the three 2,3′-dihydroxybenzamide groups are substituted into a benzene ring rather than the macrocyclic lactone. In addition various substitutions were made.[1188] The ability of these compounds to support the growth of *E. coli* K12 under iron-limited conditions and also to protect against colicin B was studied. Growth was observed with certain of these modified siderophores, notably the models with the unsubstituted 2,3-dihydroxybenzene ring, which also protected against colicin B. This was not the case with the model with a sulfonated benzene ring. These results suggest that the tricatechol–iron(III) centre is specifically recognized by the receptor site on the protein, in accord with the transport activity of both cyclic and linear enterobactin analogues. Growth was also

observed with *FepA* mutants lacking the receptor protein in the outer membrane. This may mean that amounts of the Fe^{III} analogues sufficient to support growth passed through the outer membrane. However, *FepB* mutants deficient in the iron complex-translocating system did not grow. This shows that, for *E. coli*, active transport of the siderophore–iron complex into or across the cytoplasmic membrane takes place.

The transport or release of iron has been much discussed. One view is that the iron is transferred from the siderophore complex at the outer membrane to another membrane-bound protein, for example in the uptake of iron by rhodotorulic acid in *Rhodotorula*. The other view is that the intact Fe^{III}–siderophore complex is taken up into the cell. This is supported by studies with inert chromium(III) complexes in *E. coli* and also by labelling studies.

Particular discussion has centred around the mechanism of release of the iron, in view of its high affinity for the siderophore. A very attractive proposal is that this simply involves the reduction of the Fe^{III}–siderophore complex. Iron(II) has much lower affinity for the siderophore, and so can be released: values of log K for Fe^{II} are about 8. Good evidence has been found for siderophore reductase activity in bacteria and fungi.[1198] Reduction of Fe^{III}–hydroxamate siderophores can occur readily under physiological conditions.

The release of iron from catechol siderophores is less well understood, as reduction of Fe^{III}–enterobactin (−750 mV) by physiological reducing agents seems unlikely. Accordingly, it has been suggested that the Fe^{III}–enterobactin must undergo hydrolysis before reduction, which means that the ligand cannot be recycled. A similar argument has been put forward for Fe^{III}–parabactin. The reduction potential is −673 mV at pH 7, while that of Fe^{III}–parabactin A is around −400 mV. It is suggested, therefore, that intracellular release of iron from parabactin may occur by hydrolysis of the Fe^{III}–parabactin to the more easily reducible Fe^{III}–parabactin A.[1199] The need for the degradation of enterobactin has been challenged. Mössbauer, ESR and titration experiments have shown that iron complexes of enterobactin and synthetic analogues remain as Fe^{III} between pH 2 and 10. But in methanol solution at low pH, there appears to be a quasi-reversible redox reaction, possibly reduction of the protonated Fe^{III}–enterobactin complex by the catechol group to give a semiquinone radical.[1186] This offers a mechanism for cellular removal of iron from catechol siderophores without having to degrade the siderophore structure. It should be noted that while the inability to recycle the siderophore seems wasteful, there is good evidence that the hydroxamate siderophore ferrochrome is also modified into an *N*-acetyl form of low affinity for iron,[1200] and so cannot be reused.

The transport process is unclear. In some cases it is inhibited by uncoupling agents, suggesting that uptake is linked to the electrochemical proton gradient, while evidence has also been found for a symport mechanism involving ferrichrome and Mg^{2+}.[1201]

62.1.11.3.6 Microbial iron transport and infections in animals and plants

Microorganisms in higher organisms compete for iron with transferrin and various iron-containing molecules. There is a good correlation between the virulence of pathogenic infections and the extent of siderophore synthesis, often aerobactin.[1202] Thus, one role of transferrin is to protect against infection by denying iron to invading organisms. Lactoferrin in milk and conalbumin in eggs have a similar role. The siderophore pseudobactin synthesized by soil organisms is able to stimulate the growth of the plants they invade by strongly complexing iron, so inhibiting the growth of the plant pathogen, *Erwinia*.

The competition between transferrin and infectious organisms is a fascinating topic. During infection, the mammalian host will attempt to diminish the iron available to the bacterium. The iron levels in the blood decrease and the iron stores in the liver increase. The observation that siderophore synthesis is sharply reduced at temperatures just over 37 °C may mean that the physiological function of fever is to depress bacterial siderophore synthesis, as shown for a rabbit pathogen, *Pseudomonas multocida*.[1203]

62.1.11.4 The Storage of Iron in Microorganisms

The possible role of the mycobactins in the storage of iron in the mycobacteria has been noted. Of greater significance is the identification of ferritin-like molecules in some bacteria. The cytochrome $b_{557.5}$ from *Azotobacter vinelandii*, known to be associated with large amounts of iron, is now known to be a ferritin, with an iron content of 13–20% and an electron-dense core of

55 Å diameter. This is suggested to be a store of iron for the synthesis of nitrogenase.[1204] Cytochrome b_1 from *E. coli* is also recognized to be a bacterioferritin, and has 24 subunits.[1205]

62.1.11.4.1 Magnetotactic microorganisms

Certain aquatic bacteria are influenced by the magnetic field of the earth.[1206] These magnetotactic organisms synthesize small crystals of magnetite, Fe_3O_4.[1207] The swimming direction of the bacteria is thus controlled by the magnetic field. The intracellular iron grains in *Aquaspirillum magnetotacticum* are observable by electron microscopy. They are enclosed by a membrane that is close to the cytoplasmic membrane, and may be contiguous with it. The grains are single crystals of hexagonal prismatic shape, with lattice spacings appropriate for magnetite.[1208] Each cell contains about 20 cubic-octahedral magnetosomes averaging 420 Å each side and arranged in a chain.[1209] The particles were within the single magnetic domain range for magnetite. *A. magnetotacticum* synthesizes magnetite in the presence of an iron source and when O_2 is growth-limiting. The cells are sensitive to oxygen. The addition of catalase allowed aerobic growth of the cells without the formation of magnetosomes. It is possible that formation of magnetite results from a protection mechanism against H_2O_2 through the removal of iron which would catalyze the decomposition of peroxide. An important result comes from Mössbauer spectroscopy, which has shown the presence of ferritin and the magnetite in magnetosomes.

There is increasing evidence for the occurrence of magnetotactic bacteria and algae.[1206] This has considerable biochemical significance, and suggests that fine-grain magnetic iron compounds in nature may be of microbial origin. It is difficult to be certain of the physiological function of this phenomenon, other than, perhaps, to direct the swimming direction of the organisms down towards sediments.

62.1.11.5 Transport and Storage of Iron in Plants

A number of low molecular weight chelating agents occur in plants, and have been termed 'phytosiderophores'. These compounds are suggested to be involved in the stimulation of iron uptake, and, for example, the biosynthesis of chlorophyll. An example is mugineic acid (Figure 50), which is an amino acid possessing an iron-chelating activity, from root washings of *Herdeum vulgare*. It is capable of solubilizing Fe(O)(OH) in the pH range 4–9. However, the iron-solubilizing action is strongly inhibited by divalent transition metal ions, suggesting that mugineic acid does not show selectivity towards Fe^{III}. Structures have been reported for the Fe^{III}, Co^{III}[1210] and Cu^{II}[1211] complexes. The ligand is hexadentate, with the in-plane donor atoms being the two nitrogen atoms and terminal carboxylate oxygens, with the OH and intermediate carboxylate providing the axial ligands. It is noteworthy that this compound does not resemble the microbial siderophores. This, coupled with the lack of selectivity towards iron, makes a physiological role for mugineic acid seem unlikely.

Storage of iron in plants involves phytoferritin.[1211a]

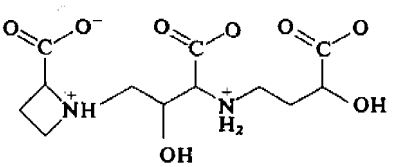


Figure 50 Structure of mugineic acid

62.1.11.6 Transport and Storage of Transition Metals other than Iron in Microorganisms

The uptake of nickel by *Clostridium pasteurianum* and *Methanobacterium bryantii* has been considered in Section 62.1.7.

There is a great deal of information available on the surface binding of transition metals to cell walls. Such cell walls possess many charged groups, such as peptidoglycan, which can contribute carboxylate groups, and teichoic acids, which provide anionic clusters due to the

presence of phosphodiester residues. There is good evidence that some cations bind much more strongly to isolated cell walls than others.[1212-1215] This selectivity is being exploited in the use of microorganisms to recover metal ions from solution. Furthermore, it appears likely that binding of metal ions to Gram-negative organisms may well have been involved in the laying down of mineral deposits, serving as a matrix for deposition.[1213,1216]

The binding of metal ions to cell surfaces will be the first stage in uptake. There is little known about the mechanisms by which metal ions are then translocated into cells. Highly specific pathways have been found for manganese in all organisms examined, so that organisms are able to concentrate Mn^{2+} even in the presence of much higher levels of Ca^{2+} and Mg^{2+}, as noted for *Bacillus subtilis* sporulation (Section 62.1.3.3.4). The *E. coli* uptake system for Mn^{2+} has a K_m value of 0.02 μmol dm^{-3} and so is readily saturated. It is unaffected by a 100 000-fold excess of Mg^{2+} and Ca^{2+}, and, while Co^{2+} is a competitive inhibitor, other transition metals are not taken up by this pathway.[1217] Mn^{2+} may also be cotransported with citrate, while low affinity mechanisms are also known. Despite the demonstration of these pathways it is difficult to demonstrate manganese requirements for growth in many cases.

The metals copper, chromium and cobalt also appear to be essential for growth for some, if not all, microorganisms.[1218] Cobalt is an essential requirement for cobalamin-utilizing bacteria, but apart from being an alternative substrate for an Mg^{2+} transport system, there appears to be no highly specific transport system for Co^{2+}. *E. coli* has a high affinity uptake system for cyanocobalamin, even though it does not require B_{12}. Cobalamin may thus serve as a source of cobalt.

62.1.11.6.1 Uptake of molybdenum

Molybdate is taken up by nitrogen-fixing organisms, which require it for synthesis of nitrogenase. Uptake is inhibited by sulfate and tungstate. *Bacillus thuringiensis*, when growing on iron-deficient medium, secretes a yellow, low molecular weight compound that reacts with sodium molybdate to give a molybdenum–peptide complex. This appears to be analogous to a siderophore.[1219] Similar results have been found to occur in molybdenum-limited *Azotobacter vinelandii*.[1220] The accumulated molybdenum is bound in a storage protein. An equivalent situation holds for tungsten when the organism is grown in the presence of tungstate. The molybdenum storage protein from *A. vinelandii* is a tetramer of two pairs of different subunits binding a minimum of 15 Mo per tetramer.[1220a]

62.1.11.6.2 The storage of copper. Microbial metallothioneins

It is now well established that microorganisms synthesize metallothionein or metallothionein-like proteins in response to high concentrations of copper, zinc or cadmium. Fungal metallothioneins seem to contain copper exclusively. A metallothionein from yeast binds 10 Cu^{+} per molecule of protein of molecular weight 10 000.[1221] The protein from *Neurospora crassa*[1222] contains only 25 amino acid residues, of which seven are cysteine residues. The protein corresponds to the seven cysteine residues of the N-terminal region of mammalian metallothioneins. It is unlike the mammalian metallothioneins in that it binds six copper atoms per molecule, probably in a single cluster.[1223] The [Cu]/[cysteine] value is very high. A copper metallothionein which contains four Cu^{I} and eight cysteine residues per molecule of protein (molecular weight 4800) has been isolated from yeast.[1223a]

Pseudomonas putida growing on 3 mM cadmium synthesizes three cysteine-rich proteins of molecular weight 4000 to 7000, containing four to seven cadmium, zinc and copper atoms per molecule. The use of ^{113}Cd NMR on the major cadmium protein shows it to be related to cadmium metallothionein, but with some significant differences.[1223b]

62.1.12 DIOXYGEN IN BIOLOGY

The oxygen molecule is a substrate for over 200 enzymes.[1224] These enzymes fall into two main categories, oxygenases and oxidases.

Oxygenases catalyze reactions in which the atoms of the oxygen molecule are incorporated into oxidized organic substrates. In dioxygenases, both oxygen atoms are inserted into the

substrate, while in monooxygenases only one oxygen atom is inserted, the other being reduced to water.

Oxidases catalyze electron transfer to dioxygen, which is reduced to superoxide, peroxide or water.[1225-1226] The best characterized example of an oxidase is cytochrome oxidase, the last member of the respiratory chain, which catalyzes the four-electron reduction of dioxygen to water.

Dioxygen, although a powerful oxidizing agent, is kinetically inert, and in general requires activation by binding to a reduced metal centre, which will be either Fe^{II} or Cu^{I}. The requirement for activation in this way allows the possibility of controlling the reactivity of dioxygen in its biological reactions. Activation involves the transfer of electron density from the reduced metal to the oxygen molecule. Control of this process, *i.e.* the extent to which such electron transfer occurs, will be one factor that dictates the biological function of the hemoprotein or other enzyme, and so determines whether it will function as an oxidase or an oxygenase, or indeed as a reversible transporter of dioxygen. The products of partial reduction of dioxygen (superoxide, hydrogen peroxide and hydroxyl radical) are not subject to kinetic control in their reactions and are, therefore, vigorous oxidizing agents. If they remain bound to the metal, then their reactivity is controlled. However, these species, particularly hydroxyl radical, may be liberated in solution or may be generated free by other reactions of dioxygen. Such reactive oxidizing agents may have a number of harmful effects. In nature, there are defences against these compounds, namely the superoxide dismutases, catalase and the selenium-dependent glutathione peroxidase,[1226,1228,1229] which all catalyze their disproportionation or reduction to dioxygen.

The requirement for dioxygen as the final acceptor of electrons in cellular respiration in aerobic organisms is usually met by diffusion of dioxygen from the surface. In larger organisms this is not feasible, and so systems for the transport and storage of dioxygen have been developed. These include hemoglobin, which has been remarkably well studied. It has been pointed out,[1230] however, that biologically speaking, hemoglobin is only an auxiliary in the process of cell respiration, and that the general significance of cytochrome oxidase greatly exceeds that of hemoglobin.

In the following sections, examples of all the classes of reaction given above will be discussed, with emphasis on those that have been well studied. Many of the enzymes involved in these processes are hemoproteins, but non-heme prosthetic groups are important in oxygenases and are also present in some oxidases. Copper is an important metal in this context, and is present in the oxygen transport protein hemocyanin, and in oxidases such as cytochrome oxidase and laccase. Some flavoenzymes are important too, but will not be covered in this discussion.

62.1.12.1 The Chemistry of Dioxygen

This is discussed by Hill and Tew in Chapter 15.2 (Volume 2). The oxygen molecule is a paramagnetic diradical, with the unpaired electrons occupying the degenerate antibonding π-orbitals. Addition of electrons to the antibonding orbitals is shown in equation (59), and results in the formation of superoxide (paramagnetic, bond order $1\frac{1}{2}$) and peroxide (diamagnetic, bond order 1). Addition of a third electron results in cleavage of the O—O bond to give oxide and hydroxyl radical, while complete reduction to water occurs on addition of a fourth electron.

$$O_2 \xrightarrow{e^-} O_2^- \xrightarrow{e^-} O_2^{2-} \xrightarrow{e^-} O_2^{3-} \xrightarrow{2H^+} O^- + H_2O \xrightarrow[2H^+]{e^-} 2H_2O \qquad (59)$$

As noted earlier, there is a kinetic restriction on the reactivity of dioxygen, as the one-electron reduction to superoxide is unfavoured. This is demonstrated in the redox potentials shown in Figure 51. The triplet ground state of the molecule may also impose spin restrictions on its reactions.

Partially reduced dioxygen species are utilized in the reactions of various enzymes. Thus, monooxygenases may use bound superoxide, while cytochrome P-450 utilizes bound peroxide in its hydroxylation reactions.[1231]

The extent of reduction of dioxygen and the use of reactive intermediate species in enzymatic reactions in the hemoproteins are determined largely by the nature of the axial ligand provided by the protein, and by other more subtle effects. The nature of the axial ligand can determine the extent to which charge is transferred to the dioxygen bound in the second axial position, through the nature of its σ-donor and π-acceptor properties. In cytochrome P-450, the axial ligand is a thiol group, which will supply electron density to the iron, and enhance electron transfer to the dioxygen. In the case of hemoglobin the axial group is imidazole, which is a good σ-donor and π-acceptor, and so can prevent excessive, irreversible transfer of electron density to the dioxygen.

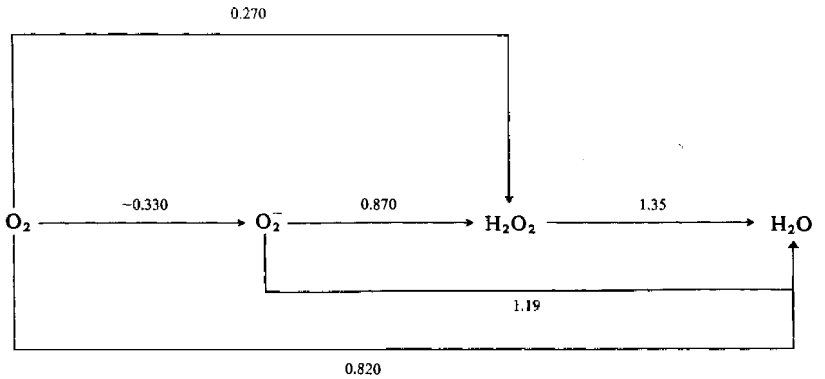


Figure 51 Reduction potentials (V) in the reduction of dioxygen at 25 °C and pH 7

62.1.12.2 Multimetal Centres and Concerted Electron Transfer

A notable feature in certain oxidases is the presence of multimetal centres. The O_2-reducing site in the oxidases that catalyze the reduction of dioxygen to water always involves two metal ions. This allows the concerted transfer of two electrons to dioxygen, giving peroxide as the first intermediate in the reduction, and avoiding the thermodynamically unfavoured production of superoxide. This has the added advantage of bypassing a toxic species. The reduction of peroxide to water then follows. Examples of such oxidases are cytochrome oxidase, and the copper proteins laccase, ascorbate oxidase and ceruloplasmin, which contain four or eight metal centres. Coupled binuclear copper sites for binding dioxygen are also found in hemocyanin, the dioxygen-binding protein of molluscs and arthropods, and tyrosinase, an enzyme which shows monooxygenase activity in the hydroxylation of monophenols, and oxidase activity in the oxidation of *ortho*-phenols. In both cases dioxygen is present as a bound peroxide group.

A different type of concerted reaction involves the bacterial cytochrome *c* peroxide, where two hemes are coupled together, so that hydrogen peroxide undergoes a two-electron reduction to water without the formation of radical species. In a number of dioxygenases, dioxygen is reduced to peroxide by concerted electron transfer from [2Fe-2S] and non-heme Fe^{II} centres.

62.1.12.3 Transport and Storage of Dioxygen

A number of well-known and much-studied iron- or copper-containing molecules are involved in these processes. Hemoglobin and myoglobin are tetrameric and monomeric hemoproteins, respectively, which bind one molecule of dioxygen at each heme iron(II) centre. Leghemoglobin is another monomeric hemoprotein found in *Rhizobium*-infected, nitrogen-fixing root nodules, while erythrocruorin is an extracellular giant hemoglobin found in various invertebrates. Hemerythrin is a non-heme iron protein from certain marine worms, which binds O_2 reversibly to give violet oxyhemerythrin with Fe/O_2 in a 2/1 ratio. Hemocyanin is the copper-containing pigment of crab blood which also binds O_2 to give blue oxyhemocyanin, with copper present as Cu^{II} and Cu/O_2 in a 2/1 ratio. Both hemerythrin and hemocyanin are colourless in the deoxy form. All these carriers or storers of dioxygen can be oxidized to the Fe^{III} or Cu^{II} 'met' forms, in which they are not active.

These carriers provide sites at the transition metal centre for the reversible attachment of dioxygen. In simpler metal complexes these metals would be irreversibly oxidized by O_2 to the thermodynamically favoured Fe^{III} or Cu^{II} state. In some way, therefore, the protein prevents the irreversible oxidation of the metal centre.

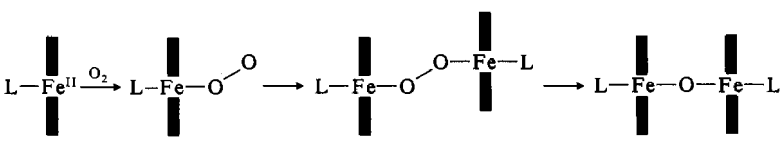
Myoglobin has a greater affinity for dioxygen than does hemoglobin, which is necessary to allow the transfer of dioxygen from the carrier hemoglobin to myoglobin for use in respiration in muscle cells. The uptake of dioxygen by hemoglobin is complex, due to interactions between its four subunits. Each subunit in hemoglobin contains a heme group and binds dioxygen reversibly. The subunits interact cooperatively, so that uptake of dioxygen by one of them enhances the affinity of the others for dioxygen. The ratio of successive binding constants is 1:4:24:9. This phenomenon is essential for hemoglobin to function efficiently, to ensure that its binding capacity

is fully utilized, and that all the bound dioxygen is released under conditions of low dioxygen concentration. Thus hemoglobin will be fully saturated in the lungs and completely deoxygenated in the capillaries. The extent of cooperativity is measured by the Hill coefficient, n. For myoglobin and isolated subunits of hemoglobin, $n = 1$, while for hemoglobin, $n = 2.8$. The value for hemerythrin is about 1.2, suggesting that it is a storage system. The origin of the cooperative effect in hemoglobin is a subject of much interest.

62.1.12.3.1 Model compounds for heme dioxygen carriers

A wide range of transition metal complexes will carry dioxygen reversibly.[1] In all cases, electron transfer takes place from the metal centre to the antibonding π-orbitals of the bound dioxygen. In some cases the bound dioxygen appears to be present as superoxide and in others as peroxide [as shown by $\nu(O_2)$ values around 1100 and 800 cm^{-1} respectively].

Of greatest interest are those compounds that attempt to model hemoglobin directly. Simple iron(II) porphyrins are readily autoxidized first to superoxo species, then to μ-peroxo dimers and finally to μ-oxo dimers, as represented in equation (60). Bridge formation must be prevented if carrier properties are to be observed. This has been achieved by the use of low temperature and sterically hindered or immobilized iron(II) porphyrins. Irreversible oxidation is also hindered by the use of hydrophobic environments. In addition, model porphyrins should be five-coordinate to allow the ready binding of O_2; this requires that one side should be protected with a hydrophobic structure. Attempts have also been made to investigate the cooperative effect by studying models in which different degrees of strain have been introduced.



(60)

Wang[1232] developed the first example of an Fe^{II} porphyrin having dioxygen-carrying-properties, namely a heme-imidazole mixture in a polymer matrix. He attributed this largely to the hydrophobic environment produced by the polymer, but another important feature was the immobilization of the heme group.

A good number of iron(II) porphyrins have been synthesized which have special structural features designed to facilitate reversible binding of O_2 without competing oxidation. Some of these are represented schematically in Figure 52, namely the 'capped' porphyrin,[1233] 'picket-fence'

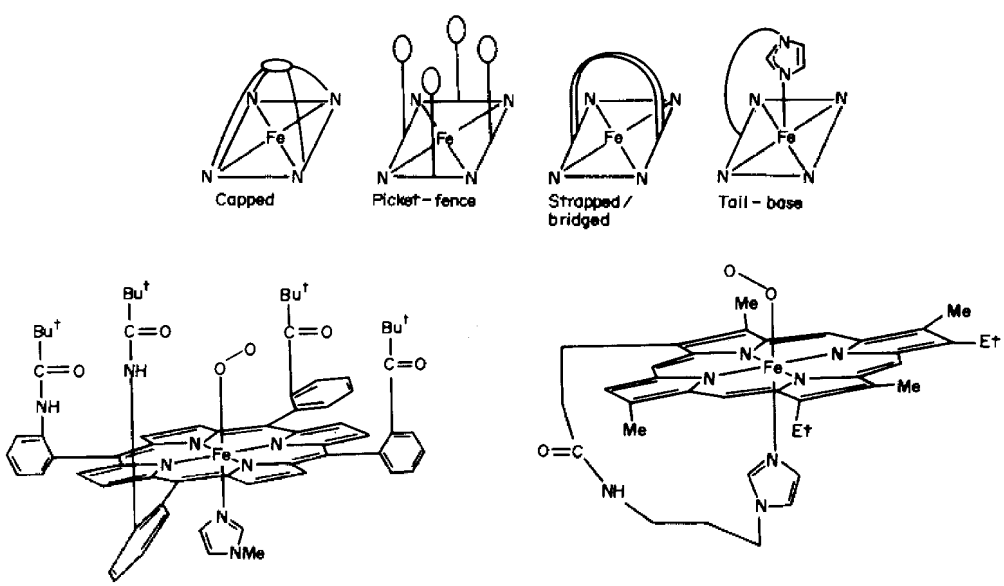


Figure 52 Some synthetic iron(II) porphyrins which function as models for dioxygen carriers

porphyrin,[1234] 'strapped' porphyrin,[1235] in which opposite *meso* positions are linked, and 'tail-base' porphyrin.[1236] Other examples are cyclophane hemes,[1237] 'tailed picket fence',[1238] 'basket handle',[1239] 'gable',[1240] 'pocket'[1241] and 'face-to-face'[1242] porphyrins. Over this range of synthetic analogues and hemoproteins, there is a dramatic variation in O_2 affinities (over a range of 10^6 in equilibrium constant). This reflects the nature of the binding site pockets, the effects of solvation, local polarity, hydrogen bonding and the effect of the protein.[1237,1243,1244] Only a few of these, notably the 'picket-fence' and 'capped' porphyrins, bind O_2 reversibly at room temperature. Several solid complexes with picket-fence porphyrins have been isolated, and the structure has been reported[1245] for Fe(TpivPP)(NMeimid)(O_2) where TpivPP = $\alpha,\alpha,\alpha,\alpha$-tetrapivaloylamidophenylporphyrin and NMeimid = *N*-methylimidazole. This shows end-on binding of O_2, with an FeOO angle of about 130°. The $\nu(O_2)$ frequency has been assigned at 1159 cm^{-1}, confirming the $Fe^{3+}(O_2^-)$ formalism. Resonance Raman spectra show the Fe-O_2 stretching frequency at 568 cm^{-1}, close to the value in oxyhemoglobin (567 cm^{-1}).

62.1.12.3.2 Hemoglobin[1246]

X-Ray diffraction data of high resolution are available for a number of hemoglobins and myoglobins, due to the work of Perutz and Kendrew and their colleagues.

Hemoglobin is a tetramer of molecular weight 64 450, and is made up of two identical pairs of units (the α- and β-units) arranged roughly in a tetrahedron. In each subunit the iron is complexed to protoporphyrin IX, with one axial ligand, an imidazole of a histidine residue, giving a five-coordinate species, although there is a loosely bound water molecule near to the sixth position. A large fraction of the protein has the α-helical structure. All the polar groups of the protein are on the outside of the molecule, with a resulting hydrophobic interior that will contribute to the stability of the Fe^{II} with respect to oxidation to the met form. In addition to the heme-imidazole link, there are other heme-protein interactions that will stabilize the structure. Thus, each heme group of oxyhemoglobin is in van der Waals contact with about 60 atoms of the protein. Further stabilization results from the interaction of the carboxyl groups of the porphyrin with basic groups of the protein, and from the interaction between the vinyl groups of the heme and the aromatic amino acids of the hydrophobic interior.

The oxygen affinity of hemoglobin varies with the pH of the medium. This is the Bohr effect, and arises from the effect of pH on the interaction between the heme and the ionizable groups of the protein. It appears that the Bohr effect is linked to the presence of a second imidazole group (the distal imidazole group), which is involved in uptake of dioxygen in some indirect way.

Uptake of O_2 is associated with substantial conformational changes, which are central to an understanding of the cooperative effect. These conformational changes are associated with the reversible interconversion of a tensed (T), low affinity form of hemoglobin into a relaxed (R) high affinity form.

The addition of dioxygen to hemoglobin is also associated with a change in the magnetic properties from paramagnetism to diamagnetism. Perutz[1247] has an explanation of long standing for the cooperative effect in hemoglobin, which accommodates the magnetic data and is based on an earlier suggestion by Hoard.[1248] This is represented in Figure 53.

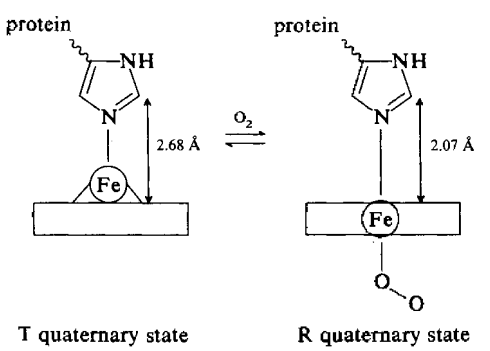


Figure 53 The trigger for the cooperative effect in hemoglobin

The deoxy form of hemoglobin is high-spin and paramagnetic, with the iron(II) lying above the plane of the heme, due it was suggested to its large size, which prevented its moving into the cavity in the porphyrin. Binding of O_2 results in the formation of low-spin iron(II), which is smaller and can move into the plane of the heme. The bound dioxygen (present as O_2 in this hypothesis) must be in an excited singlet state to give a diamagnetic species. The resulting movement of the iron atom relative to the plane of the porphyrin is magnified through the interactions in hemoglobin, so that substantial conformational changes occur.

This view of the trigger effect is now thought to be at least partly incorrect. There have been several demonstrations of the occurrence in solution and in the solid state of high-spin iron porphyrins which are six coordinate, and which have the Fe^{II} lying in the plane of the porphyrin ring.[1249] Thus the movement of the iron(II) in hemoglobin cannot be attributed directly to the high-spin–low-spin electronic rearrangement. Rather, it is to be expected that a five-coordinate complex would have the metal ion displaced out of the basal plane towards the axial ligand. Formation of a six-coordinate complex will remove this effect.

There is also some uncertainty on the extent of movement of the iron with respect to the porphyrin plane. The original X-ray data indicated that in deoxyhemoglobin the iron lies some 0.56 Å above the porphyrin plane and moves to a position in or close to the plane in oxyhemoglobin. Earlier EXAFS data on deoxyhemoglobin have been interpreted to show that the iron atom lies only 0.2 Å above the porphyrin plane.[1250] However, Perutz *et al.*[1251] have published a further assessment of EXAFS data on deoxyhemoglobin, and have compared this with data on a picket-fence porphyrin, where the displacement of the iron from the porphyrin plane was known to be about 0.4 Å. It is claimed that there is a similar displacement of the iron in deoxyhemoglobin. It appears, therefore, that there is a substantial movement of the iron with respect to the porphyrin plane on oxygenation of hemoglobin, but its relationship to the cooperative effect awaits elucidation.

A further problem centres on the nature of the $Fe(O_2)$ group. It is known that dioxygen is bound end-on (in oxymyoglobin) with an FeOO angle of 121°. The Pauling model accounts[1252] for the diamagnetism of oxyhemoglobin in terms of low-spin Fe^{II} with $^1O_2$. However, Weiss[1253] has suggested that oxyhemoglobin involves a superoxide complex of Fe^{III}, $Fe^{III}(O_2^-)$. The diamagnetism results from strong antiferromagnetic interaction between low-spin iron(III) and superoxide. In support of Weiss's view, it should be noted that $\nu(O_2)$ has been assigned at 1107 cm^{-1} in oxyhemoglobin (clearly in the range expected for superoxide); that superoxide may be displaced from oxyhemoglobin by weak nucleophiles such as chloride; that addition of superoxide ion to met(Fe^{III}) hemoglobin gives oxyhemoglobin; and that there are similarities between oxyhemoglobin and a range of other oxyhemoproteins that do involve $Fe^{III}(O_2^-)$. These arguments are not conclusive, and support has been expressed for the $Fe^{II}(O_2)$ view.[1254,1255]

It is, however, of interest to consider coboglobin, formed by recombination of the globin from hemoglobin with the cobalt-substituted protoporphyrin.[1256] The coboglobins take up O_2 reversibly, showing cooperative and Bohr effects. The deoxycoboglobin involves low-spin cobalt(II), so allowing the application of ESR techniques. The hyperfine splitting from the Co^{II} is coupled with that from the nitrogen donor atom from the axial imidazole group, showing that the unpaired electron occupies the d_{z^2} orbital. In the oxy derivative, the nitrogen hyperfine splitting disappears and the separation of the hyperfine lines due to cobalt is reduced to about a third. This shows that the unpaired electron has been largely transferred from the cobalt, giving $Co^{III}(O_2^-)$. Further confirmation comes from ESR studies on $CoHb^{17}O_2$, which show hyperfine splitting due to the nuclear spin of ^{17}O ($I = \frac{5}{2}$), confirming therefore that the unpaired electron density is transferred from the Co^{II} to O_2. It appears that some 60% of the electron density is transferred.[1257] The $\nu(O_2)$ mode for oxycoboglobin (1106 cm^{-1}) is very similar to that for oxyhemoglobin (1107 cm^{-1}), showing that the argument based on the cobalt derivative may be applied to hemoglobin.

ESR studies also show the similarity between oxycoboglobin and oxygenated cobalt porphyrin, and suggest that the protein does not measurably influence the electronic structure of the heme group, although the protein does control the extent to which dioxygen is bound.

The magnetic properties of hemoglobin have been reinvestigated, and the claim made[1258] that it is paramagnetic at room temperature, although such paramagnetism is not shown in the NMR spectrum. These conclusions have now been challenged,[1259] and evidence presented for the complete diamagnetism of both oxy- and carbonmonoxy-hemoglobin. Thus, at present, while it is not possible to give a definitive assessment of the electronic distribution in oxyhemoglobin, the balance of current evidence seems to support strongly its formulation as an Fe^{III} superoxide species.

62.1.12.3.3 The cooperative effect in hemoglobin

This effect results from the transition between two alternative structures, the tensed (T) low affinity form and the relaxed (R) high affinity form. Binding of dioxygen at one heme must trigger a stereochemical change, which then sets in motion the transition from the T to the R form. The constraints in the protein which oppose this change result in the low affinity of the T structure. This conformation change induces the T → R conformation change in the remaining vacant O_2-binding sites in the tetramer, so that O_2 affinity increases as more O_2 is bound and the R conformation is stabilized to a greater extent.

The movement of the iron atom into the plane of the porphyrin on binding of dioxygen means that the proximal (axial) histidine has to move possibly up to 0.4 Å towards the porphyrin plane. Perutz has suggested that the low affinity for dioxygen showed by the T structure is due to constraints provided by the protein which oppose this movement of the proximal histidine. The stereochemical nature of these constraints has been established[1260] by a detailed comparison of the structures of human deoxyhemoglobin, human carbonmonoxyhemoglobin and horse methemoglobin.

Transition from the T to the R structure does not involve significant changes in the contact between the components of the $\alpha\beta$ dimer. The change in quaternary structure results rather from large changes in the association of the $\alpha_1\beta_1$ dimer with the $\alpha_2\beta_2$ dimer.

A number of differences in tertiary structure between T and R forms have been found. The hemes lie in pockets in the protein, into which they are wedged tightly by about 16 side-chains. These allow no movement of the iron atom and its axial histidine ligand relative to the plane of the porphyrin without a change in the tertiary structure of the protein. Furthermore, in the β-subunits of the T structure, the site for dioxygen is obstructed by the distal valine residue, and this too can only be cleared by a change in tertiary structure. The detailed differences in tertiary structure are shown in the paper of Baldwin and Chothia,[1260] and are beyond the scope of this account. Particularly important effects are manifested in the orientation of the proximal histidines. In deoxyhemoglobin the imidazole rings are in asymmetric positions with respect to the hemes. The imidazole plane is approximately normal to the heme, but is tilted in its own plane. This feature is intrinsic to the T structure, and prevents the imidazole group moving towards the porphyrin plane. The iron atom can only move into the plane of the porphyrin if the tilt can be removed, which is accomplished on switch to the R form. Theoretical investigations on the most likely change in conformation of the heme complex on oxygenation and the pathway of its transmission to the subunit boundaries have attributed the restraint to oxygenation in the T structure as the tilt of the proximal histidines.[1261]

Thus it appears that the affinity for dioxygen is controlled by restraint of the movement of the heme iron and by steric hindrance of the ligand site.

The chemical viability of the first proposal is confirmed by studies on model porphyrins, where the axial imidazole group is hindered to prevent movement towards the plane of the porphyrin. Thus, binding of dioxygen to iron(II) picket-fence porphyrins with *N*-methylimidazole as an

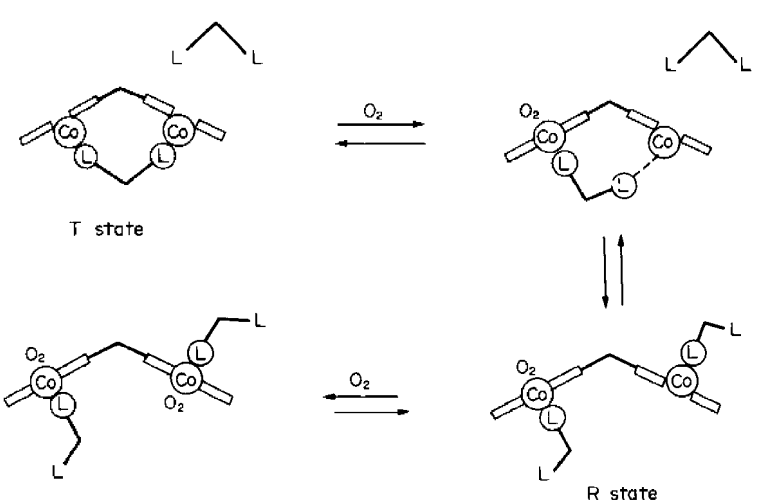


Figure 54 Cobalt(II) gable porphyrins—a model for the cooperative effect

axial ligand is similar to that with myoglobin and isolated subunits of hemoglobin. But the use of 1,2-dimethylimidazole as the axial ligand causes a decrease in affinity for dioxygen, down to the level of hemoglobin (T). The ratio of oxygen affinities for *N*-methyl- and 1,2-dimethyl-imidazole as axial ligands is 80:1, quite similar to the ratio of 100:1 observed for R and T hemoglobin. Close contact between the 2-methyl group and the porphyrin nitrogen hinders the approach of the imidazole and its attached iron to the porphyrin plane.[1262] Similar conclusions have been found using 'tail-base' hemes, where strain can be built into the chelation arm.[1257] By shortening the arm linking the imidazole to the porphyrin (see Figure 52), it is possible to introduce a tilt into the axial imidazole group, as found in R state hemoglobin. The presence of such strain lowers affinity for O_2.[1263]

Cooperative binding of dioxygen has been demonstrated[1264] in cobalt(II) 'gable' porphyrin model compounds, where structural change at one porphyrin, produced by binding of O_2, is manifested in enhanced affinity at the other porphyrin. The gable porphyrin (Figure 54) involves two triphenylporphyrin groups bridged by a common phenyl group, with the axial positions filled by a bridging *N,N'*-diimidazolylmethane ligand. The deoxy complex has reduced affinity for O_2, due to the lowered ability of the cobalt to move into the plane of the porphyrin. However, the resulting in-plane coordination of the cobalt on oxygenation is manifested in a weakened Co–ligand bond in the second porphyrin, so that the bridging *N,N'*-diimidazolylmethane is lost and free ligand binds from the other side. Dioxygen then binds with higher affinity. The Hill coefficient is estimated to be 1.5. Such experiments as these confirm the feasibility of dioxygen-binding affinity being reduced by steric constraints, and then being increased on removal of the constraint.

The R → T transition in hemoglobin may be brought about by a number of allosteric effectors,[1265] such as H^+, Cl^-, CO_2 and inositol hexaphosphate, which function either by strengthening salt bridges between subunits or by forming additional ones. Such salt bridges are broken on oxygenation. The control of the structure of hemoglobin by the use of such effectors has been of value in the comparison of structural features in R and T hemoglobin derivatives by various instrumental techniques. Criteria have been established for distinguishing between the two quaternary forms by techniques such as Raman, NMR, CD, MCD and UV spectroscopy.[1246,1266,1267]

62.1.12.3.4 Monomeric and dimeric hemoglobins

These include mammalian myoglobin, the hemoglobins of the lamprey, sea-snails and clams, and leghemoglobin. The tertiary structure of all these species is similar to that of sperm whale myoglobin, the first protein structure to be solved, and which has now been determined as various liganded forms at resolutions down to 1.5 Å.[1268] Data on oxymyoglobin show that the O_2 is bound end-on with a bent configuration, as originally suggested by Pauling, with an FeOO angle of 121°, and that the iron is out of the plane by 0.33 Å. The position of the O_2 in the heme pocket is fixed, being constrained by steric hindrance from phenylalanine, valine and distal histidine residues. Neutron diffraction data show that the bound dioxygen is hydrogen bonded to the distal histidine.[1269] The myoglobin from *Aplysia limacina* provides an example of a myoglobin with some different features. Thus, the distal histidine is missing, and the metal site is more accessible to the solvent.

Leghemoglobin,[1270] from nitrogen-fixing nodules in *Rhizobium*-infected legumes, is a monomeric hemoprotein which shows high affinity for O_2. It functions in part as a buffer to control dioxygen levels in the nodule and so prevent damage to the nitrogenase enzyme. This high affinity results from a combination of an extremely fast O_2 on-rate constant ($k' = 118\ dm^3\ \mu mol^{-1}\ s^{-1}$) and a moderately slow O_2 off-rate constant ($k = 4.4\ s^{-1}$), giving an equilibrium dissociation constant $K = k/k' = 37\ nmol\ dm^{-3}$. The affinity of myoglobin for dioxygen is much lower than this with $K = 530\ nmol\ dm^{-3}$. In myoglobin, as noted above, there seems to be a tight compartment around the dioxygen-binding site, while in leghemoglobin there appears to an unusually large and accessible distal cavity in which the distal histidine group can move freely. The cavity appears to collapse partly as O_2 is bound, so that inward movement of distal histidine towards the bound O_2 might, by steric hindrance, account for the relatively slow O_2 off-rate and the stability of the Fe—O_2 bond.

The rate of dissociation of dioxygen is dependent upon pH, with a pK value of 5.46.[1271] Furthermore, ESR studies[1272] on cobalt leghemoglobin, in addition to confirming the presence of the proximal histidine group as a ligand,[1273] show a pH-dependent spectrum with apparent pK about 5.7. In both cases the pH-sensitive group is suggested to be the distal histidine (His-61).

The pH dependence of the rate of dissociation of dioxygen is attributed to a hydrogen bonding nteraction between the bound dioxygen and the protonated distal histidine group. As the pH ncreases, so the rate of dissociation increases as the extent of protonation of the histidine falls. The rate varies by a factor of 5 from acid to alkaline limits. In contrast, the rate of dissociation of dioxygen from oxymyoglobin is independent of pH, and there appears to be a hydrogen bond from the distal histidine at all pH values. The formation of the hydrogen bond in oxyleghemoglobin decreases the rate of dioxygen dissociation, and so gives rise to a pH dependence of the dioxygen affinity, which is very unusual for a monomeric hemoglobin. This may well be of some biological significance.

Some dimeric myoglobins have been isolated from the muscles of the sea-snail *Nassa mutabilis* and from the clams *Anadora broughtonii* and *A. senilis*. These have no Bohr effect but show cooperative effects for the uptake of O_2.[1274]

62.1.12.3.5 Giant hemoglobins

Extracellular hemoglobins are widely distributed among annelids, molluscs and arthropods. They are large proteins, made up in some cases of two superimposed hexagonal discs, some 250 Å in diameter, each containing six subunits. The molecular weights of the subunits lie in the range 20 000 to 29 000 for erythrocruorins and from 25 000 to 35 000 for chlorocruorins. Dissociation into subunits occurs mainly at pH values above pH 8. The extent of association of the subunits has effects upon the behaviour of erythrocruorin.[1275]

The structure of erythrocruorin has been refined to 1.4 Å resolution.[1276] The oxy form binds O_2 with a bent geometry and an enhanced FeOO angle of 150°. Of particular interest is the fact that the Fe atom is displaced slightly more from the plane of the heme in oxy- (~0.3 Å) than in deoxy-erythrocruorin (~0.2 Å). This may be due to the presence of a water molecule that is hydrogen bonded to the bound O_2. Thus spin-state changes are not necessarily linked to pronounced movements of the metal atom.

62.1.12.3.6 The reversible binding of dioxygen by hemoproteins

It is now possible to summarize the various contributions made by protein and heme in the binding of dioxygen. The protein provides a five-coordinate deoxy state and a hydrophobic environment which enhances the binding of O_2 and prevents irreversible oxidation to the met form. It also provides the constraints on the movement of the axial histidine group relative to the plane of the porphyrin that are linked to the origin of the cooperative effect in hemoglobin. The axial histidine group, in addition to providing heme–globin interaction, also controls electron distribution in the $Fe(O_2)$ grouping, through its strong σ-donor and π-acceptor properties. The role of the distal imidazole group is being clarified. The interaction between this group and the bound O_2 species is enhanced by the charge transfer to the dioxygen to give, effectively, bound superoxide ion. This specific interaction probably contributes to the selectivity of the binding site for dioxygen. These observations help to explain why the same heme is used in nature for so many different functions by being attached to different proteins.

62.1.12.3.7 Hemerythrin

Hemerythrin is a non-heme iron protein used in the transport and storage of dioxygen by several phyla of marine invertebrates, notably the sipunculid worms.[1277] Deoxyhemerythrin is colourless or pale pink, and becomes violet on oxygenation. Hemerythrin from erythrocytes of the worm *Golfingia gouldii* has a molecular weight of about 108 000, and is made up of eight identical subunits, each of which contains two iron atoms and binds one oxygen molecule. Examples are known in which hemerythrin is trimeric, dimeric and tetrameric. Myohemerythrin is found in muscle tissue, and is a monomeric species analogous to the hemerythrin subunit. Oxymyohemerythrin is more stable than oxyhemerythrin, as expected from the analogy with hemoglobin and myoglobin.

Deoxyhemerythrin contains two Fe^{II} centres which react with dioxygen to give two Fe^{III} centres with bound peroxide. This process occurs with only little cooperativity, the value of the Hill coefficient lying in the range 1.0 to 1.4. Oxyhemerythrin undergoes autoxidation in solution to

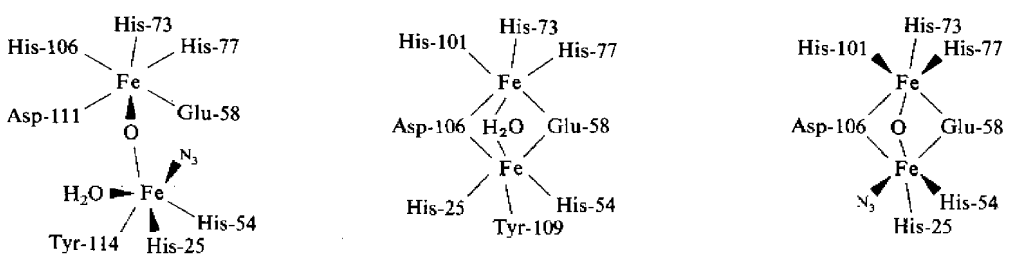
give the iron(III) 'met' form, which does not react with O_2. However, the met form combines with a range of anions, where the anion probably binds at the O_2 site. The oxy → met transformation is accelerated by anions. These reactions are summarized in equation (61). It should also be noted that semi-met forms of hemerythrin can be prepared in which the iron centres are formally Fe^{III} and Fe^{II}. Two relatively stable species can be prepared either by one-electron reduction of methemerythrin or by one-electron oxidation of deoxyhemerythrin. Both species undergo disproportionation, as shown in equation (62).[1278]

$$\underset{Fe^{II},\,Fe^{II}}{\text{deoxy}} + O_2 \rightleftharpoons \underset{Fe^{III},\,Fe^{III},\,O_2^{2-}}{\text{oxy}} \xrightarrow{L} \underset{Fe^{III},\,Fe^{III},\,L^-}{\text{met}} + O_2^{2-} \tag{61}$$

$$(Fe^{II}Fe^{III})_8 \rightarrow (Fe_2^{II})_4(Fe_2^{III})_4 \tag{62}$$

Deoxyhemerythrin is paramagnetic, having two high-spin ($S = 2$) Fe^{II} centres. The presence of iron(III) centres in oxyhemerythrin is shown by the similarity between the electronic spectra of oxyhemerythrin and the met form. Resonance Raman spectra show a band at 848 cm^{-1} assigned to $\nu(O_2)$, as shown by studies with $^{18}O_2$, which is appropriate for a peroxo group. Use of $^{16}O—^{18}O$ shows that the two atoms of the peroxide have different environments,[1279] while the iron(III) centres have different environments also, as indicated by the Mössbauer spectra of oxyhemerythrin. These observations are consistent with a structure for oxyhemerythrin in which the peroxide is bound end-on to one iron centre only.

Earlier X-ray structures have given conflicting data on the nature of the iron binuclear site[1280–1282] for metazido- and methydroxo-hemerythrin, but the situation has been clarified by a determination at 2.2 Å resolution of the structure of metazidohemerythrin from *Themiste dyscritum*.[1283] All three structures are given in Figure 55, while the subunit arrangement is shown schematically in Figure 56.



Metazidomyohemerythrin from *T. zostericola* | Methydroxohemerythrin from *T. dyscritum* | Metazidohemerythrin from *T. dyscritum*

Figure 55 Structures for the binuclear iron centre in hemerythrin

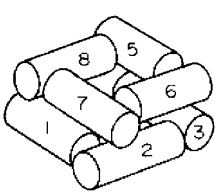


Figure 56 The arrangement of the subunits in hemerythrin

The most recent structure of the metazidohemerythrin (Figure 55c) shows that each iron is octahedrally coordinated, with the iron centres bridged by carboxylate groups from Asp-106 and Glu-58 and by an oxo group. The remaining coordination positions are filled by three histidine side-chains in one case and two histidines and the azide ion in the other. The azide group probably fills the O_2-binding site in the oxyhemerythrin, again suggesting that O_2 is bound end-on. Methydroxohemerythrin has an empty coordination site, so that one iron is five-coordinate. The structure of the azide complex was predicted previously on spectroscopic grounds.[1284] There is some uncertainty over the nature of the bridging group, but spectroscopic and magnetic evidence, which shows antiferromagnetic interactions between the two iron(III) species, is consistent with an oxo bridge.[1285] It should also be noted that similar Fe_2 sites are found in other proteins, where

there is evidence for oxo bridges. These include ribonucleotide reductase and purple acid phosphatase, discussed in Section 62.1.5.5.

The postulate of an oxo bridge is also supported by EXAFS data,[1286,1287] which show that the oxo bridge is present in oxyhemerythrin and metazidohemerythrin, but possibly absent in hemerythrin. This work also shows that the peroxide group in oxyhemerythrin is bound at the azide site in metazidohemerythrin, and that one of the iron centres in deoxyhemerythrin may be five-coordinate.

Prior to these structural studies, work using chemically modified proteins had shown the requirement for at least four histidine ligands per subunit together with a glutamic acid residue and Tyr-109 (Tyr-114 in met). The most recent X-ray work has eliminated the possibility that Tyr-109 is a ligand, a possibility proposed in earlier X-ray work. Other work on chemical modification of residues has been reviewed.[1277]

The quaternary structure (Figure 56) has been described as a square doughnut, $75 \times 75 \times 40$ Å^3, with an open central cavity 20 Å in diameter. Each iron site is about 28–30 Å from its two neighbours in the same layer. The amino acid residues involved in the hydrogen bonds and salt bridges between subunits have been identified in *T. dyscritum*. These residues are largely absent from myohemerythrin, which is in accord with its monomeric character. The arrangements of subunits from other oligomeric forms of hemerythrin have been established. Thus the trimer subunits from *Siphonosoma funafuti* are arranged in a triangle.[1288]

62.1.12.3.8 Hemocyanin

The hemocyanins bind and transport dioxygen in many species of the Mollusca and Arthropoda phyla. They are very large molecules, and are often made up of more than 100 subunits with molecular weights between 25 000 and 75 000. The hemocyanin of *Loligo pealei* has a molecular weight of 3 750 000. Some smaller hemocyanins are known. Thus the horse shoe crab *Limulus polyphemus* has a unique 48-subunit hemocyanin made up of eight immunochemically distinct subunits.[1289] Two related Chelicerata, the scorpion *Androctonus* and the spider *Eurypelma* have 24-subunit hemocyanins that crosslink immunochemically with *Limulus* hemocyanin, and yet do not give the 48-subunit oligomer. The 48-subunit oligomer in *Limulus* hemocyanin results from specific stabilization by calcium ions, which must crosslink negative groups to prevent dissociation. If Ca^{2+} is removed, then the hemocyanin undergoes rapid dissociation to monomers *via* 24- and 12-subunit intermediates. The factors that govern the assembly and stabilization of such large molecules as the hemocyanins and the erythrocruorins are of general relevance to the function of biopolymers.

Each subunit in hemocyanins contains a pair of copper atoms which bind one oxygen molecule. The deoxy protein is colourless while the oxy form is blue, showing the oxidation of Cu^{I} to Cu^{II} on oxygenation. In addition to bands at 440, 570 and 700 nm, an intense band is observed at 347 nm in the spectrum of oxyhemocyanin, which is assigned to charge transfer between the two copper centres or between Cu^{II} and peroxide. Resonance Raman spectra of several oxyhemocyanins show $\nu(O_2)$ at about 745 cm^{-1} indicative of a bound peroxo group. The oxyhemocyanin is completely diamagnetic and ESR-silent, showing antiferromagnetic interaction between the copper centres ($-2J = 550$ cm^{-1}).

EXAFS data on *Busycon canaliculatum* oxyhemocyanin have been interpreted[1290] in terms of a model having two copper atoms, separated by 3.67 Å, each bound to three histidine ligands, and bridged by the peroxo group and an atom from a protein ligand, possibly a phenolate from tyrosine. Analysis of EXAFS data on oxyhemocyanin of *Megathura crenulata* and the α- and β-components of *Helix pomatia* shows[1291] only two histidine ligands and two low Z atoms (N or O) per copper, with Cu—Cu separation of 3.55 Å. The copper is present in approximately square planar geometry, and one of the low Z atoms will be the peroxide oxygen. The model for the oxyhemocyanin site is shown in Figure 57. The possibility of bridging peroxide bound through one oxygen atom only is eliminated by resonance Raman measurements which show the peroxide atoms to be equivalent. The EXAFS results for deoxyhemocyanin[1292] confirm that copper is coordinated to two histidines each, and provide no evidence for Cu···Cu interaction within 4 Å and some evidence for a Cu···Cu distance of 5.6 Å. The coordination number of copper (two) is low for a metalloprotein, but this does allow facile binding of dioxygen. On oxygenation, the two copper atoms become oxidized to Cu^{II}, move towards each other (to 3.55 Å), and become bridged by the low Z ligand atom, with the bridging peroxide bound at the binuclear site. Thus oxygenation must involve some reorganization of the protein.

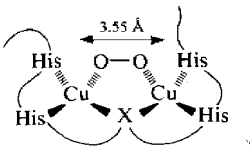


Figure 57 Model for the active site in oxyhemocyanin

The results of other studies have contributed to the elucidation of the active site of hemocyanin. Thus, imidazole groups have been suggested to be ligands by the use of UV-vis and Raman spectroscopy, acid-base titrations and photooxidation studies. Methemocyanin is formed on oxidation of hemocyanin, in which case an exogenous bridging ligand will replace peroxide. These bridging ligands mediate the antiferromagnetic interaction. The nature of the endogenous bridging ligand has been the subject of much discussion. The possibility that it is an oxygen atom would be appropriate for strong antiferromagnetic interaction, but a tyrosine group[1293] now seems unlikely on a number of grounds. An alternative group is alkoxide from serine or threonine residues,[1294] although their pK_a values (>16) are quite high.

The binuclear site in hemocyanin seems to be very similar to that in tyrosinase (Section 62.1.12.11.2). A detailed analysis of their electronic structures has been prepared,[906] particular attention being paid to the two intense spectral features which dominate the UV-vis region, namely the bands at 347 nm ($\varepsilon \approx 20\,000\ dm^3\ mol^{-1}\ cm^{-1}$) and 570 nm ($\varepsilon \approx 1000$). Elucidation of these unique spectral features is complicated considerably by the binuclear nature of the site. One approach has been to prepare a series of hemocyanin (and tyrosinase) active site derivatives, beginning with the simplest derivative, met-apo, where one copper has been removed and the other oxidized to Cu^{II}, and then preparing others of increasing complexity such as the mixed valence 'half met' forms. The two dominant spectral features are not present in methemocyanin, suggesting they can be assigned as $O_2^{2-} \rightarrow Cu^{II}$ charge transfer. Resonance Raman measurements on oxyhemocyanin with laser excitation into either of the two intense bands produce an enhanced Raman peak at $\sim 750\ cm^{-1}$. When $^{18}O_2$ is substituted for $^{16}O_2$, the peak shifts to $\sim 710\ cm^{-1}$, confirming the vibration to be due to $\nu(O_2)$ for peroxide. This confirms that the absorption bands are $O_2^{2-} \rightarrow Cu^{II}$ charge-transfer transitions. In the CD spectrum of oxyhemocyanin an additional $O_2^{2-} \rightarrow Cu^{II}$ charge-transfer transition is seen. The observation of at least three $O_2^{2-} \rightarrow Cu^{II}$ CT bands requires that peroxide bridges the two coppers. The band at 440 nm may well be (endogenous bridge) $\rightarrow Cu^{II}$ charge transfer.

The binding of CO to hemocyanin is of interest. The two-coordinate copper centres in deoxyhemocyanin might each be expected to bind CO. However, some two-coordinate complexes of Cu^{I} with heterocyclic donor ligands show lack of reactivity towards CO in the absence of additional ligands, probably because the metal does not receive enough electron density to 'back bond' to CO.[1295]

62.1.12.4 Cytochrome Oxidase

Cytochrome oxidase is a membrane-bound enzyme that accepts electrons from cytochrome *c*, and transfers them to dioxygen in the respiratory chain. The dioxygen undergoes a four-electron reduction to water. The importance of cytochrome oxidase amongst O_2-utilizing enzymes is emphasized by the fact that it is probably responsible for more than 90% of the total consumption of dioxygen by living organisms.

Cytochrome oxidase also serves as a proton pump, so that the process of electron transfer is associated with the vectorial transfer of protons across the membrane, and thus contributes to the establishment of the proton gradient which is used to drive the synthesis of ATP. Cytochrome oxidase is located in the inner mitochondrial membrane of animal, plant and yeast cells (the eukaryotes) and in the cell membrane of prokaryotes. The arrangement is represented schematically in Figure 58. The complexity of cytochrome oxidase and the problems associated with its solubilization from the membrane have presented great obstacles to the elucidation of the structure and mechanism of the enzyme, but its importance has resulted in an enormous literature, which has been reviewed frequently.[1296–1299]

Mammalian cytochrome oxidase has attracted particular attention. It contains four redox-active transition metal centres, two type *a* cytochromes (*a* and a_3) and two copper ions. Other oxidases

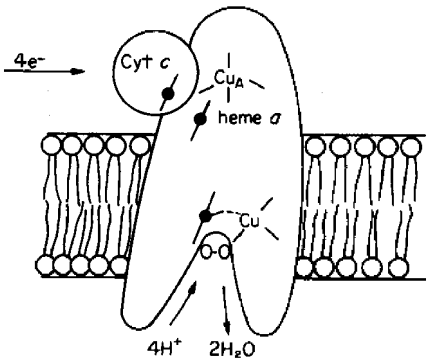


Figure 58 Schematic representation of the arrangement of the redox centres in cytochrome oxidase

that reduce dioxygen to water also have four redox metal centres; thus laccase contains four copper centres, appropriate for a four-electron reduction reaction.

It has been suggested that cytochrome a_3 and one of the copper centres are antiferromagnetically coupled as they are both undetectable by ESR techniques in the oxidized enzyme. It is thought that the cytochrome a_3 and the copper (Cu_B) share a common ligand, which has been suggested by various authors to be oxide, hydroxide, sulfide and imidazolate. The other centres, cytochrome *a* and Cu_A, are isolated and may be detected by ESR in the Fe^{III} and Cu^{II} states.

Cytochrome *a* is usually low-spin and six-coordinate, and will therefore be involved in electron transfer. Cytochrome a_3 is high-spin and five-coordinate, and is therefore able to bind small molecules such as O_2 and CO in the sixth, axial position when present as Fe^{II}. It appears therefore that cytochrome a_3 is the component of cytochrome oxidase that binds dioxygen, and it is possible that at some stage the dioxygen species would bridge the a_3 iron and Cu_B.

The close proximity of the a_3 and Cu_B centres has been demonstrated for the low-spin oxidized cyanide complex, where the cyanide acts as a bridging ligand between a_3 and Cu_B.

The temperature dependence of the paramagnetic susceptibility of oxidized cytochrome oxidase over the ranges 200–7 K[1300] and 4.2–1.5 K[1301] has been interpreted in terms of a model with two isolated $S=\frac{1}{2}$ centres (low-spin Fe^{III} and Cu^{II}) and a spin-coupled $S=2$ centre (high-spin $Fe^{III}\cdots Cu^{II}$). Additional information has been provided by MCD studies[1302,1303] on the oxidized low-spin complex with cyanide bound to the a_3 heme. This work shows that the cyanide is a bridging ligand to copper. Saturation curves have been observed for the a_3 Soret MCD signal, showing that the a_3–CN–Cu_B centre cannot have a diamagnetic ground state. The data suggest an $S=1$ ground state, which has been interpreted[1303] in terms of ferromagnetic coupling between Cu_B ($S=\frac{1}{2}$) and a_3–CN^- ($S=\frac{1}{2}$). The alternative of Fe^{IV} and Cu^I seems unlikely. It is difficult to reconcile these two sets of results, but the MCD work seems to be clear cut in its essential conclusion of an $S=1$ ground state. Near-IR CD and MCD experiments also suggest that it is unlikely that a blue copper centre is present in cytochrome oxidase. Some considerations that support the opposite view will be given later.

62.1.12.4.1 Structure and organization

As noted, cytochrome oxidase spans the inner mitochondrial membrane. One side is exposed to the outer surface and accepts electrons from ferrocytochrome *c*. The inside face contains the cytochrome a_3–Cu_B pair. Mitochondrial cytochrome oxidase is reported to contain from six to twelve different subunits. It is generally accepted that the three largest polypeptides are true subunits of the enzyme, but it is still not certain how many of the other subunits fall into this class. The two largest subunits are suggested to be associated with the redox centres, and the third (III) to have a specific role in the translocation of protons. Subunit III is not involved in the catalysis of electron transfer. Amino acid sequencing has been carried out for a number of these subunits. Subunit II of beef heart cytochrome oxidase has a region that shows[1304] considerable homology with the 'blue' electron-transfer copper protein plastocyanin, and contains two cysteine, one histidine and one methionine residues which could represent a binding site for copper. An interesting comparison may be made at this stage with certain bacterial oxidases[1305] which closely resemble mitochondrial cytochrome oxidase. Many of these appear to have a much simpler subunit

composition. The cytochrome oxidase from *Paracoccus denitrificans* appears to have only two subunits (molecular weights 45 000 and 28 000), heme *a*, heme a_3 and two copper ions.[1306] These subunits resemble the subunits I and II of the mitochondrial enzyme, showing similar properties with respect to activity and spectra. This suggests strongly that subunits I and II of the mitochondrial enzyme contain all four redox centres. Subunit II provides the binding site for cytochrome *c*, and probably contains heme *a* in addition to a copper site. There is some evidence that heme a_3 is present in subunit I.[1299]

The interaction of cytochrome oxidase with lipids is essential for its biological function, and has therefore been widely studied in order to explore the topological arrangement of the subunits in membranes.[1307] Subunit III is suggested to span the membrane, as required for the role of III in proton translocation, subunit I is buried in the membrane and II extends into the cytosol. The orientation of the heme groups with respect to the membrane has been studied using orientated multilayers, and measuring the angular dependence of the ESR spectrum. It appears that the heme planes are perpendicular to the membrane surface.[1308]

Some progress has been made in the characterization of the redox centres. The presence of a potential type 1 blue copper site in subunit I is in accord with EXAFS data that have demonstrated Cu—S interactions, in particular the possibility of two sulfur atoms bound to Cu_A.[1309] It seems possible therefore that Cu_A is a type 1 copper, typical of copper electron-transfer proteins. The nature of Cu_B is less certain: ESR parameters indicate that Cu_B is similar to type 3 copper, which occurs pairwise in copper oxidases as the O_2-binding site.

An imidazole group of histidine has been identified conclusively as an axial ligand in cytochrome a_3. The nature of the a_3–Cu_B bridge is still unclear. EXAFS data have been interpreted[1310] in terms of a bridging thiolate ligand, but this is not yet generally accepted. Bridging imidazolate has now been eliminated,[1311,1312] partly because information from model compounds shows that such a bridge would not mediate the strong antiferromagnetic coupling ($-J > 200\ cm^{-1}$) found for cytochrome a_3 and Cu_B. Instead an oxo bridge has been suggested,[1312] formed possibly from the dioxygen. It should be noted that these difficulties in characterizing the nature of the bridging group between a_3 and Cu_B have led to the suggestion that the two centres are separate from each other, and that the magnetic properties of the oxidized enzyme result from the presence of Fe^{IV} and Cu^{I} rather than coupled Fe^{III} and Cu^{II}. However, ESR studies[1313] on the reaction of nitric oxide with cytochrome oxidase show that the oxidized enzyme contains cytochrome a_3 (Fe^{3+}) and $Cu_B{}^{2+}$ at an estimated distance of 3.4 Å from each other.

EXAFS data on the carbonmonoxy cytochrome a_3 indicate[1310] that the first shell structure is identical to that of hemoglobin, a point of some mechanistic interest.

62.1.12.4.2 Reaction mechanism

In general terms, it is assumed that the dioxygen binds to the reduced enzyme at the $a_3 \cdots Cu_B$ site (with K_m values in the range 0.3–3 μmol dm^{-3}), and is then reduced to a bound peroxo group, and subsequently to water. The details of the mechanism are the subject of much uncertainty. The reaction of dioxygen with fully reduced cytochrome oxidase is very fast, but low temperature techniques involving flash photolysis of carbonmonoxy derivatives have allowed these reactions to be studied, and individual steps to be identified. In these experiments, the fully reduced or 'mixed valence' enzyme is saturated with carbon monoxide to give the Fe^{II} a_3–CO complex. The suspension is then saturated with dioxygen, which now cannot react with the cytochrome oxidase, and further cooled to an appropriate temperature (between −130 and −60 °C). The reaction with O_2 is initiated by an intense flash of light which photolyzes the Fe—CO bond. The O_2 may then react at the empty coordination site on the cytochrome a_3, and the reaction may be followed by various techniques. This procedure was developed by Chance and his coworkers. The intermediates may represent species with increasing oxidation levels for the metal centres, or they may represent species where electronic redistribution has occurred within a particular intermediate. Useful parallel experiments involve studies of the reaction of O_2 with the 'mixed valence' oxidase where the cytochrome *a* and Cu_A are oxidized, and the other two are reduced. Again a number of intermediate species are seen in the reaction with dioxygen. It is clearly of interest to compare these two situations.

The overall picture is further complicated in that various forms of the enzyme may be prepared. The resting or fully oxidized form of the enzyme obtained in normal preparations appears to differ from the form obtained by reducing the resting enzyme and reoxidizing with molecular

oxygen. The latter species is more active, and is termed the 'pulsed oxidase'. It has been suggested that the pulsed form contains a bridging oxo group.

It is beyond the scope of this discussion to consider the complex interrelationships between these species in detail, but a clear account is given by Wikström *et al.*[1299] Instead, a summary of the intermediates formed in the reduction of dioxygen will be presented. It is probable that not all of the many intermediates observed are of mechanistic significance.

On photolysis of the reduced or mixed valence enzyme, the 590 nm band of the a_3-CO species disappears and a new band appears at 612 nm, due to the generation of five-coordinate cytochrome a_3^{2+}. If dioxygen is present, and at a temperature higher than about −100 °C, then a new species (A) is formed, which cannot be photolyzed, and which is spectrally similar to the a_3^{2+}–CO compound. It is probable that this involves O_2 bound to the cytochrome a_3, and does not involve bridging a_3 and Cu_B. This species would approximate to oxyhemoglobin, and would involve some charge transfer to bound dioxygen.

The subsequent reactions differ in the cases of the reduced and mixed valence enzyme. The reaction of the mixed valence compound may well be expected to be simpler than that of the fully reduced enzyme, as electron transfer from cytochrome *a* and Cu_A cannot be involved. As the spectrum due to compound A from the mixed valence enzyme disappears, so a new band forms with maximum intensity at 605–610 nm. This is compound C, which appears to involve peroxo-bridged Fe^{III} and Cu^{II}. At one time it was thought that cytochrome a_3 in compound C was Fe^{II}, but this view seems unlikely. Another possibility involves peroxide bridging Fe^{IV} and Cu^{I}. These suggestions have all been assessed in the light of UV-vis absorption and ESR spectroscopy. They are shown in Figure 59.

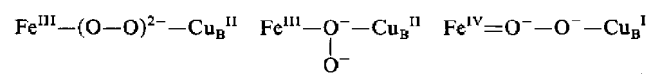


Figure 59 Possible formulations of compound C of cytochrome oxidase

The reaction of the fully reduced enzyme with O_2 does not follow the pathway described above. Instead, loss of compound A is followed by the production of compound B through the intermediate formation of another compound (II), which may be equivalent to the peroxo compound C, but having reduced cytochrome *a* and Cu_A. The transient nature of this species II compared to compound C would result from the possibility of electron transfer from cytochrome *a* and Cu_A, to give compound B. The fact that cytochrome *a* and Cu_A are at least partially oxidized in compound B is shown by the appearance of the ESR signal (in 30–50% intensity) characteristic of the fully oxidized enzyme. Intermediates beyond compound B in the oxidation sequence have also been described. In one of these, the Cu_B^{2+} is ESR-detectable.

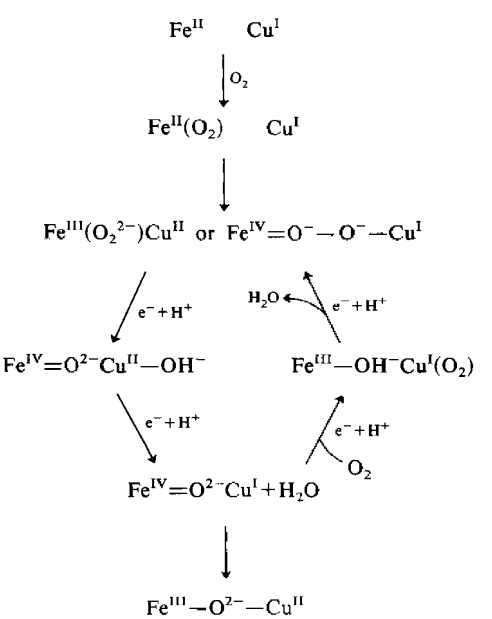


Figure 60 A scheme for the reduction of O_2 at the a_3/Cu_B centre of cytochrome oxidase

Some insight into the understanding of these later intermediates comes from the observation that the fully oxidized enzyme may undergo a one-electron oxidation reaction, in which the electron donor is probably water and the acceptor ferricytochrome *c*. The overall product would be a one-electron oxidation product of the fully oxidized centre plus water. Presumably, one-electron reactions in the opposite direction can occur. The transfer of one electron from cytochrome *a* to the a_3/Cu_B centre in compound C, plus one electron from a_3 or Cu_B will allow a second concerted two-electron reaction with the formation of ($Fe^{IV}=O^{2-}Cu_B^{II}—OH^-$), and ESR visibility of the copper. In the next stage of the reaction antiferromagnetic coupling would be reintroduced.

A mechanism has been put forward by Wikström *et al.*[1299] in which reduction of O_2 occurs in two concerted two-electron steps, but with electron transfer to the a_3/Cu_B centre occurring by discrete one-electron steps. The latter feature is suggested to allow the coupling of the redox reactions of cytochrome *a* to proton translocation. They suggest that the two possible forms of the fully oxidized enzyme correspond to the 'pulsed' (ferryl iron) and resting (μ-oxo) states of the enzyme (Figure 60). The addition of the third electron to the bridging peroxide species will result in a breaking of the O—O bond and the formation of hydroxide. Rapid electron transfer from the Fe^{III} to the remaining fragment gives oxide rather than O^-, and effects a two-electron reduction of peroxide. The formation of a ferryl ion is consistent with the ESR signal for the Cu_B^{2+} ion, which shows interaction with a nearby paramagnetic ion.[1313] The formulation $Fe^{III}(O^-)$ would be diamagnetic, while the ferryl ion would be paramagnetic.

62.1.12.4.3 Electron-transfer pathways in cytochrome oxidase

The present view is that cytochrome *a* is the acceptor of electrons from cytochrome *c*, but that a simple linear electron-transfer sequence from cytochrome *a* to Cu_A and then to the cytochrome a_3/Cu_B centre is unlikely. Instead the sequence shown in equation (63) holds, where cytochrome *a* is in rapid equilibrium with Cu_A. These views depend largely upon pre-steady-state kinetics of the redox half reactions of the enzyme with its two substrates, ferrocytochrome *c* and O_2. However, these conclusions are not in accord with kinetic studies[1314] under conditions when both substrates are bound to the enzyme, and which show maximal rates of electron transfer from cytochrome *c* to O_2. In particular some of the cytochrome *c* is oxidized at a faster rate than a metal centre in the oxidase. In contrast, at high ionic strength conditions, where the cytochrome *c* and the cytochrome oxidase are mainly dissociated, oxidation of cytochrome *c* occurs only slowly following the complete oxidation of the oxidase. These results for the fast oxidation of cytochrome *c* have been interpreted in terms of direct electron transfer from cytochrome *c* to the bridged peroxo intermediate involving a_3^{3+} and Cu_B^{2+}, or to a two-electron transfer to O_2 from cytochromes *a* and a_3 during the initial phase of the reaction.

$$\begin{array}{l} c \rightarrow (a) \rightarrow (Cu_B, a_3) \rightarrow O_2 \\ \quad\quad \uparrow\downarrow \\ \quad\quad Cu_A \end{array} \qquad (63)$$

The interaction of cytochrome oxidase with cytochrome *c* has been considered in Section 62.1.5.2.5.

62.1.12.5 Bacterial Cytochrome Oxidases

Bacterial cytochrome oxidases offer an interesting area of study that complements well that of mitochondrial cytochrome oxidase. In some cases they are readily solubilized from the membrane; they tend to have fewer subunits than the mitochondrial oxidase; and they form stable intermediates during the reaction with dioxygen. They often do not have a role in energy transduction, a fact reflected in their simpler structures.

Poole[1305] has reviewed the bacterial cytochrome oxidases, and has drawn attention to features which are not present in the mitochondrial enzyme, and which reflect the metabolic diversity and adaptability of bacteria. These are: (1) the synthesis of the oxidases is controlled dramatically by the prevailing environmental conditions; (2) some oxidases are multifunctional, and may use electron acceptors other than dioxygen; (3) more than one type of oxidase may be present, each terminating a branched electron-transfer pathway.

62.1.12.5.1 Cytochrome oxidases of the aa_3 type

These are similar to the mitochondrial enzyme, apart from the simpler subunit composition. EXAFS studies[1310] on the oxidases from *Paracoccus denitrificans* and *Thermus thermophilus* have confirmed the metal centres to be similar to those in the mitochondrial enzyme. In the latter case, the ESR silent cytochrome a_3 in the reduced enzyme has been shown by the use of Mössbauer spectroscopy to involve five-coordinate, high-spin Fe^{II}.[1315] On addition of cyanide to the oxidized enzyme, there is evidence for a low-spin Fe^{III} complex with cyanide, and for coupling to the Cu_B centre. One of the advantages of microbial systems is that ^{57}Fe-enriched enzymes may readily be obtained by growing the organism on a medium supplemented with ^{57}Fe.

A non-covalent complex that contains cytochromes c_1 and aa_3 and has a molecular weight of about 93 000 has been isolated from *T. thermophilus*. This contains two proteins only, cytochrome c_1 and a protein of molecular weight about 55 000 which is though to be a single subunit cytochrome oxidase containing the two cytochromes and two copper centres.[1316] The use of a thermophilic organism often allows membrane-bound enzymes to be extracted, as their stability is greater. It is of great interest that a single subunit cytochrome oxidase has been isolated, although the two peptides in this complex cannot be separated from each other. Preliminary studies on the cytochrome c_1aa_3 complex have been reported.[1317]

Cytochrome caa_3 has also been purified from the thermophile PS3, and appears to be a three-subunit complex.[1318,1319]

62.1.12.5.2 Cytochrome o

This cytochrome oxidase ('o' is an abbreviation for oxidase) is widely distributed and may completely or partly replace cytochrome oxidase aa_3 under conditions where the supply of dioxygen is limited. It is a membrane-bound enzyme which has proved difficult to purify, and whose spectral characteristics are those of *b* cytochromes. Its identity is usually confirmed by observation of the distinctive spectral features of its complex with carbon monoxide.

The cytochrome *o* from *Azotobacter vinelandii* is reported to consist of one polypeptide of molecular weight 28 000 with two identical heme components. It has also been isolated from the thermophile PS3,[1319] *Escherichia coli*, *Vitreoscilla*, *Pseudomonas aeruginosa*, and *Rhodopseudomonas* spp. The enzyme from *Vitreoscilla* consists of two identical polypeptides of molecular weight 13 000 and two moles of protoheme IX. A cytochrome b_{562}-*o* complex from *E. coli* contains two peptides and, strangely, copper.[1320]

Cytochrome *o* binds dioxygen with K_m values in the range 1.8–6.5 μmol dm^{-3}. Addition of dioxygen to the reduced cytochrome *o* from *Acetobacter suboxydans* gave a species assumed to be a stable oxygenated intermediate, which on further oxidation gave the oxidized form. Stable intermediates are also given by cytochrome *o* from *Vitreoscilla*. The IR spectrum of the oxygenated form shows[1321] absorptions at 1134 cm^{-1} due to bound dioxygen. The assignment was confirmed by the use of $^{18}O_2$, and the observation of a shift in frequency to 1078 cm^{-1}. This value is appropriate for a bound superoxide group, *i.e.* Fe^{III} (O_2^-), and is similar to $\nu(O_2)$ for oxyhemoglobin. Formation of the oxidized enzyme from the reduced form requires 0.5 mol O_2 per mol cytochrome, and there is spectral evidence for the formation of an intermediate prior to the oxygenated form. The tight binding of superoxide in the oxygenated form limits any toxic effects. The final product is hydrogen peroxide, as shown in equation (64).

$$b^{2+}\cdot b^{2+} \xrightarrow{O_2} b^{2+}(O_2)b^{2+} \rightarrow b^{2+}(O_2^-)b^{3+} \rightarrow b^{3+}\cdot b^{3+} + O_2^{2-} \quad (64)$$

62.1.12.5.3 Cytochrome d

This is found in a range of bacteria,[1305] particularly Gram-negative heterotrophic bacteria, and often coexists with other oxidases. The production of cytochrome *d* occurs under O_2-limited or sulfate-limited conditions, and is found in obligate anaerobes. Cytochrome *d* has a chlorin prosthetic group. It occurs in *E. coli* as a complex with cytochromes b_{558} and a_1.[1322] The complex with cytochrome b_{558} has been purified.[1323]

Cytochrome *d* has a remarkable affinity for dioxygen, with K_m values in the range 0.018–0.35 μmol dm^{-3}. Thus, it could be synthesized by anaerobes as a defence mechanism against O_2, which would be scavenged by cytochrome *d*. It will also be synthesized at low dioxygen levels

by aerobes, as it will be able to maintain respiration under low-O_2 conditions. Cytochrome *d* also appears to confer lack of sensitivity to cyanide. Normally cyanide binds at the open coordination position of five-coordinate hemes. In this case, the affinity for O_2 is so high that cyanide cannot compete for the site. Thus *Achromobacter* in the presence of 1 mmol dm^{-3} KCN shows adaptive growth and respiration that may be correlated to the increased appearance of cytochromes a_1 and *d*, particularly the latter oxidase.

Low temperature trapping techniques involving photolysis of the CO-liganded cytochrome *d* in the presence of dioxygen have produced evidence for an intermediate species which has been suggested to be an oxygenated intermediate analogous to oxyhemoglobin.[1324] This is confirmed by resonance Raman experiments on the solubilized and aerated enzyme from *E. coli*, which show features at 1078–1105 cm^{-1} that may be assigned to $\nu(O_2)$ of the oxygenated oxidase.[1325]

62.1.12.5.4 Cytochrome cd_1

The cd_1 oxidase from *Pseudomonas aeruginosa* has been most extensively studied. Both hemes are low-spin in the oxidized protein, while heme *c* is diamagnetic and d_1 is high-spin, probably five-coordinate, in the reduced state.[1326] The enzyme is associated with the inner surface of the cytoplasmic membrane, but is readily solubilized, an unusual feature. Molecular weight determinations suggest that the enzyme is a dimer, each subunit having *c* and d_1 hemes. It is suggested that all four hemes are at one end of the dimer, a suggestion that is of important mechanistic significance.[1327]

The cd_1 enzyme may operate physiologically with compounds other than dioxygen as the terminal electron acceptor. Thus its dominant role is that of a nitrite reductase, nitrite being reduced to NO. Binding of O_2 is suggested to follow two pathways, depending upon O_2 tension. In the high oxygen tension pathway, two oxygen molecules bind to the enzyme and are reduced to peroxide, which then follows a catalase-like decomposition reaction. In the low-oxygen-tension pathway, a direct reduction of the peroxide to water occurs.[1328]

62.1.12.5.5 Terminal oxidases in the aerobic carboxydobacteria

Terminal oxidases are inhibited by small molecules and ions such as carbon monoxide, nitric oxide, nitrite and cyanide which bind tightly at the dioxygen site. It is noteworthy, therefore, that the carboxydobacteria are able to use carbon monoxide as the sole carbon and energy source, with dioxygen as the final electron acceptor. As noted earlier, the carbon monoxide oxidase from these bacteria is a molybdoprotein in which the molybdenum is bound by a pterin group. The remarkable lack of toxicity of carbon monoxide to these aerobic organisms is attributed to the presence of novel cytochrome *o* (cyt b_{563}) as a terminal oxidase, which is suggested to be insensitive to carbon monoxide.[1329] Nevertheless, it is difficult to accept that carbon monoxide cannot compete with dioxygen for the dioxygen-binding site. The question of selective binding of CO and O_2 to heme proteins and various model porphyrins has been of some interest recently, in an endeavour to pinpoint factors which may contribute to selectivity.

Normally carbon monoxide gives a linear Fe—CO group, while dioxygen gives a bent Fe—O_2 structure. It is well known that the Fe—CO group is forced to adopt a non-linear geometry in hemoproteins through interaction with various distal groups. This may lower the affinity for CO and so provide some protection for the site against CO. Attempts have been made[1330,1331] to synthesize model porphyrin compounds with pockets to accommodate bent Fe—O_2 groups, and which provide steric hindrance against the preferred linear geometry of Fe—CO. This work has led to the conclusion that there is substantially lowered affinity for CO in the sterically hindered porphyrins. Kinetic studies on the binding of O_2 and CO by cyclophane hemes[1332,1333] and cofacial diporphyrins[1333] have shown that distal steric hindrance affects the ligand association rate constant and has no effect on the dissociation rates. The association rates showed a differentiation factor against binding of CO in the range 3 to 8. However, these are not very large factors in view of the substantial differences between these models and the native oxidases. It has also been shown[1334] that changes in the electronic properties of the heme group had little effect on affinity for CO. At this stage, therefore, it is reasonable to say that distal steric effects could provide some protection against carbon monoxide toxicity towards terminal heme oxidases. It is certainly not possible to account for the remarkable resistance of the carboxydobacteria to the toxic effects of carbon monoxide. One conclusion is that the terminal oxidase in the carboxydobacteria is not a hemoprotein.

62.1.12.6 Blue Copper Oxidases

In the discussion of the biochemistry of copper in Section 62.1.8 it was noted that three types of copper exist in copper enzymes. These are: type 1 ('blue' copper centres); type 2 ('normal' copper centres); and type 3 (which occur as coupled pairs). All three classes are present in the blue copper oxidases laccase, ascorbate oxidase and ceruloplasmin. Laccase contains four copper ions per molecule, and the other two contain eight copper ions per molecule. In all cases oxidation of substrate is linked to the four-electron reduction of dioxygen to water. Unlike cytochrome oxidase, these are water-soluble enzymes, and so are convenient systems for studying the problems of multielectron redox reactions. The type 3 pair of copper centres constitutes the O_2-reducing sites in these enzymes, and provides a two-electron pathway to peroxide, bypassing the formation of superoxide. Laccase also contains one type 1 and one type 2 centre. While ascorbate oxidase contains eight copper ions per molecule, so far ESR and analysis data have led to the identification of type 1 (two), type 2 (two) and type 3 (four) copper centres.

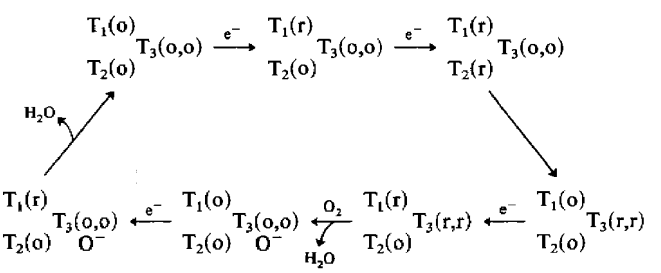
At present, understanding of these blue oxidases is limited, but progress is being made[906] towards the characterization of the metal sites, and certain features in the mechanism seem well established. This is particularly true for the laccase from *Rhus vernicifera*. The use of optical, CD, MCD and ESR spectroscopy by various workers[906,1335] has led to a description of the type 1 site as having a flattened tetrahedral geometry, with two histidines and one cysteine ligand. Histidine has also been proposed as a ligand for the type 2 site, and indeed it has been suggested[1336] that the type 2 Cu in ceruloplasmin contains three nitrogen donor ligands. EXAFS measurements exclude sulfur as a donor to the type 3 site, and lead indirectly therefore to the conclusion that a histidine group is a ligand. The ligands at the type 3 site are discussed[962] in Section 62.1.8.3.

It is possible to prepare *R. vernicifera* laccase which is reversibly depleted in the type 2 copper. This is a great aid in understanding the role of type 2 copper in the mechanism. Type 2-depleted laccase may exist with the type 3 site in the oxidized or reduced form. The spectral features of the blue type 1 copper change with change in the oxidation state of the type 3 copper. This intersite structural interaction may relate to the electron-transfer pathway between type 1 and type 3 copper.[1337] The type 2 site has been implicated in the binding of polyphenolic substrates.[959]

Solomon *et al.*[906] have suggested that the peroxide is bound to a single copper at the binuclear type 3 site, and so differs from the bridging peroxide found for hemocyanin and tyrosinase (Figure 57). Comparison with a laccase from which the type 2 copper has been removed has led to the suggestion that the type 2 copper is necessary to stabilize the type 3 Cu–hydroperoxide complex. The type 2 and type 3 centres appear to be close together, as rapid-quench ESR experiments with reduced laccase and $^{17}O_2$ have shown that the $H_2{}^{17}O$ thus formed is bound equatorially at the type 2 Cu ion.[1338]

Kinetic studies with laccase have shown that the enzyme must be reduced by the organic substrate before reaction with dioxygen occurs. The first electron from the substrate is accepted by the type 1 Cu^{2+}, and the second by the type 2 Cu^{2+}. The electrons from these reduced sites are then transferred to the type 3 copper pair, which then binds dioxygen with reduction to peroxide. It is possible that the type 2 and type 3 centres are in the same cavity, which only becomes accessible to the solvent when the type 1 Cu^{+} is oxidized.

An intermediate in the reaction has been identified. Its optical spectrum is very similar to that of the complex formed by adding hydrogen peroxide to the oxidized enzyme. However, it appears unlikely that the peroxo complex is the observed intermediate, as the optical intermediate has been identified with a paramagnetic intermediate, shown by ESR.[1339] The use of ^{17}O-enriched O_2



T_n = type of copper; o = oxidized, r = reduced

Figure 61 The mechanism of laccase

has shown unambiguously that this is an oxygen radical. It appears that after the formation of peroxide, there is a rapid transfer of an electron from the type 1 copper, so that the first observable intermediate is a three-electron reduced species. The ESR data suggest that the radical is O^-, which would be expected if three electrons are transferred to O_2.

The type 1 Cu^{2+} will immediately be re-reduced and then transfer this electron to the type 3 site, so completing the reduction of the hydroxyl radical to water. A scheme is shown in Figure 61.[1340]

Ceruloplasmin is the major copper-containing protein in mammalian blood plasma (see Section 62.1.8.5), and appears to consist of a single polypeptide chain of molecular weight 130 000.[1341] The nine-line superhyperfine splitting in the ESR spectrum of the type 2 copper has been interpreted in terms of four equivalent nitrogen ligands.[978]

62.1.12.7 Non-blue Copper Oxidases

A number of copper-containing proteins show spectral features like those of normal copper complexes, and therefore do not appear to contain 'blue' copper centres. Amongst these are galactase oxidase and the amine oxidases. It is noteworthy that it appears unlikely that the copper is involved in the activation of dioxygen.

Galactose oxidase catalyzes the oxidation of many primary alcohols to the corresponding aldehyde, with reduction of dioxygen to hydrogen peroxide.[1342] It contains one type 2 copper centre per molecule (molecular weight 68 000) and no other metal centres, and thus represents the simplest known copper protein. The Cu^{II} appears to be coordinated to two imidazole groups, one solvent water and a fourth ligand, which is non-nitrogenous, while NMR studies show that exogenous ligands can bind at two sites (axial and equatorial) with displacement of water to give a five-coordinate complex.[1343] The mechanism of reduction of dioxygen is controversial, as a two-electron reduction is linked to one redox centre. One possibility is that the copper is reduced to Cu^{I} by the substrate, and then oxidized to Cu^{III} by dioxygen, with production of hydrogen peroxide. However, galactose cannot reduce Cu^{II}, and the Cu^{II} is redox inactive in the absence of mediators. As noted above, ligand-binding sites are available on the copper centre, and galactose binds to Cu^{II} in the enzyme. Studies on the binding of fluoride in the presence of dioxygen failed to show evidence for competition between O_2 and bound fluoride.[1344] This suggests that the role of copper in galactose oxidase may only be one of binding the substrate, which then reacts directly with O_2.

The amine oxidases catalyze the oxidative deamination of biological amines as shown in equation (65). They have molecular weights greater than 100 000 and are generally composed of two subunits, each containing one copper ion. ESR and NMR studies indicate that the copper is Cu^{II} bound by at least two imidazole groups. Alternatively one ligand may be a pyridine group where pyridoxal phosphate is a prosthetic group of the enzyme. There is no convincing evidence for a role for copper in the activation of dioxygen. On the other hand copper-free amine oxidases are not enzymatically active. Bovine plasma amine oxidase reconstituted with only one Cu^{II} per molecule of protein retained full activity,[1345] suggesting only one of the two Cu sites is necessary for catalysis.

$$RCH_2NH_2 + O_2 + H_2O \rightarrow RCHO + H_2O_2 + NH_3 \quad (65)$$

In benzylamine oxidase there is evidence that the amine undergoes transamination with the pyridoxal prosthetic group to give a pyridoxamine, which is then oxidized by dioxygen to give H_2O_2 and NH_3. The role for the copper is one of activation of the substrate.[1346]

62.1.12.8 The Superoxide Dismutases

Superoxide dismutase is widespread in nature, and is suggested[1347] to have the important function of catalyzing the disproportionation of the superoxide ion (equation 66). Aerobic organisms have high levels of superoxide dismutase in accord with this view. Protection for the cell against these toxic byproducts of oxygen respiration is completed by the enzyme catalase, which catalyzes the decomposition of the hydrogen peroxide. Superoxide undergoes spontaneous disproportionation, but the catalytic effect of the superoxide dismutase is remarkable, possibly as high as a factor of 10^9.[1348,1349]

$$2O_2^- \rightarrow O_2 + O_2^{2-} \quad (66)$$

The enzyme isolated from eukaryotic sources contains copper and zinc, while those obtained from other sources may contain iron or manganese. The latter two species are closely related, as shown by extensive homologies in their amino acid sequences.[1349]

62.1.12.8.1 The copper–zinc superoxide dismutase

The best studied dismutase is that isolated from bovine erythrocytes. It has a molecular weight of 31 400 and is made up of two identical subunits each containing one copper and one zinc. X-Ray diffraction studies[1350,1351] have shown the copper to be bound by four imidazole ligands (His-44, His-46, His-61 and His-118) plus water, in a distorted five-coordinate geometry, while the zinc has a tetrahedral environment with three imidazole ligands (His-61, His-69 and His-78) and one oxygen donor (Asp-81). The residue His-61 is a bridging imidazolate group. The overall structure is represented schematically in Figure 62.

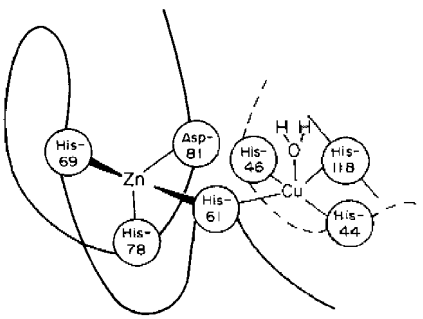


Figure 62 The structure of the Cu–Zn superoxide dismutase

Each subunit has a deep channel on the outside surface, with the Cu^{II} slightly exposed on the floor of the channel, and close to the completely buried Zn^{II}. The amino acid residues making up this channel are highly conserved in enzymes from different species, suggesting that the channel is important. The site for superoxide binding has been identified as a small pit over the Cu^{II}. This region of the enzyme is highly stabilized through an interlocking network of hydrogen bonds. The active site pit contains highly ordered water molecules. Two of them form a 'ghost' of a superoxide ion at the Cu site; one binds to the Cu, and the other to a guanidinium N of Arg-141. These two water molecules form an OOCu angle of 120°, which is the expected geometry of a bound superoxide ion.

During catalysis of superoxide disproportionation, the copper centre is reversibly oxidized and reduced by successive encounters with superoxide, giving O_2 and H_2O_2 (equations 67 and 68). The zinc(II) almost certainly has a structural role in the formation and stabilization of the active site,[1352] and indirectly in enhancing the reactivity of the copper.

$$ECu^{II} + O_2^- + H^+ \rightleftharpoons E'Cu^{I} + O_2 \quad (67)$$

$$E'Cu^{I} + O_2^- + H^+ \rightleftharpoons ECu^{II} + H_2O_2 \quad (68)$$

The detailed X-ray data have allowed an elegant elaboration of this mechanism. The protein environment with the tetrahedral distortion results in a high redox potential for the copper (0.42 V). The first catalytic reaction is facilitated by relaxation of distortions in the Zn ligand geometry found for the Cu^{II} enzyme through the bridging His-61 being allowed to rock away from the copper with copper-bridge bond breaking, when the latter is in its Cu^{I} state. The high rate enhancement brought about by the enzyme over an already fast reaction is of interest. The rate constant for superoxide dismutase is within an order of magnitude of the diffusion-controlled limit. It is evident therefore that the number of non-productive collisions between SOD and O_2^- is low. This rate enhancement has been explained[1351] by a consideration of the electrostatic potential in and around the active site channel. The presence of positively charged residues at critical positions means that the incoming negatively charged superoxide ion is guided towards the copper in the active site, with a minimization of non-productive collisions. It will be interesting to see if a similar system operates in the manganese and iron superoxide dismutases.

Both copper and zinc may be removed readily by dialysis, and replaced by four copper ions. Alternatively the zinc may be replaced by cobalt. In both cases antiferromagnetic interactions between Cu-Cu and Cu-Co have been observed. This has allowed the testing of the hypothesis that the mechanism of superoxide dismutase involves the breaking and reformation of the Cu—imidazolate bond. Lippard and coworkers[1353] have monitored the ESR spectrum of the four-copper form of the enzyme, and have detected breaking of the bridge on lyophilization by the elimination of the antiferromagnetic interaction between the copper centres. They suggest that bridge breaking results from conformational changes brought about in the protein by the loss of water of hydration. Addition of water resulted in the restoration of the ESR spectrum characteristic of the Cu-Cu coupling.

Table 27 Manganese and Iron Superoxide Dismutases

Source	*MW*	*Subunits*	*Metal/mol*	*Ref.*
Bacteria				
Bacillus subtilis	45 000	2×22 500	1.1 Mn	1
B. stearothermophilus	40 000	2×20 000	4.0 Mn	2
Streptococcus faecalis	45 000	2×22 500	1.3 Mn	3
S. mutans	42 000	2×19 000	1.2 Mn	4
Thermus aquaticus	80 000	4×21 000	2.1 Mn	5
T. thermophilus	80 000	4×20 000	2.0 Mn	6
Escherichia coli	40 000	2×20 000	1.2 Mn	4, 7
Mycobacterium lepraemurium	45 000	2×22 000	1.3 Mn	8
M. tuberculosis	88 000	4×22 000	4.0 Fe	9
Chromatium vinosum	82 000	2×41 000	2.0 Fe	10
Anacystis nidulans	37 000	2×18 500	1.0 Fe	11
Desulfovibrium desulfuricans	43 000	2×21 500	1.6 Fe	12
E. coli	39 000	2×18 000	1.0–1.8 Fe	13[a]
Pseudomonas ovalis	44 000	2×21 000	2.0 Fe	14[a]
Bacteroides fragilis	42 000	2×20 500	1.8–1.9 Fe	15
Prokaryotic algae				
Sprirulina platensis	37 000	2×18 400	1.0 Fe	16
Plectonema boryanum	37 000	2×19 000	0.94 Fe	17
Eukaryotic algae				
Porphyridium cruentum	40 000	2×20 000	2.0 Mn	18
Yeast				
Saccharomyces cerevisiae	100 000	4×25 000	3.0 Mn	19
Serratia marcescens	48 000	2×24 000	1.5 Mn	20
Animal				
Bovine heart mitochondria	86 000	4×21 500	2.0 Mn	21
Human liver	85 000	4×21 000	3.9 Mn	22
Chicken livcer mitochondria	80 000	4×20 000	2.3 Mn	4

[a] Structure determined.

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Catalysis of superoxide dismutation by the cobalt enzyme has been interpreted in terms of rapid protonation/deprotonation of the copper-facing nitrogen atom of the bridging imidazole as the Cu-bridge bond breaks, with the suggestion that the bridging imidazole may well be the proton donor in the formation of hydrogen peroxide.[1354] These conclusions are also supported by the X-ray data,[1350] which suggest that in the second step of the reaction the role of the zinc is to ensure protonation of His-61, and to position this proton correctly for hydrogen bonding and subsequent transfer to the second superoxide ion.

The X-ray data have been interpreted in terms of the binding of superoxide to Cu^{II} and to Arg-141. It is noteworthy that previous modification of arginine-141 with α,β-diketones resulted in a 90% loss of activity, and that the authors had suggested a role for Arg-141 in the binding of superoxide.[1355]

62.1.12.8.2 The superoxide dismutases with manganese or iron

These dismutases are still poorly characterized. Table 27 lists details of both iron- and manganese-containing enzymes. The manganese dismutases contain Mn^{III}, and occur either as dimers or tetramers with subunits of molecular weight about 20 000. The Mn/subunit ratio varies from 0.5 through 1.0 to 2.0. The iron dismutases have subunits of 20 000 or 40 000 and an upper limit of one Fe^{III} per subunit. It has been pointed out that most of the proteins are synthesized initially as precursors, which are between 2000 and 6000 larger in molecular weight than that of the mature protein.

The structure of the iron-containing superoxide dismutase from *Pseudomonas ovalis* has been determined at 2.9 Å resolution.[1356] This enzyme has a molecular weight of 44 000, and is made up of two identical subunits, each containing one iron atom. The subunit is roughly triangular in shape, with dimensions $52 \times 40 \times 32$ Å^3. The iron, present as high-spin iron(III), is bound by four protein ligands, including His-26, while a water molecule may also be coordinated. The precise geometry is still unclear. The iron superoxide dismutase from *E. coli* (determined to 3.1 Å resolution[1357]) appears to be identical to the *P. ovalis* iron superoxide dismutase. There is no resemblance at all to the structure of the Cu–Zn superoxide dismutase.

Similarities in amino acid composition and homologies of partial sequences show that the subunits of the iron and manganese proteins are structurally related. This is emphasized by the fact that the anaerobic bacterium *Propionibacterium shermanii* can synthesize either Fe- or Mn-containing superoxide dismutase with an apparently identical protein, dependent on the metal supplied.[1358] However, the Fe enzyme had a metal/subunit ratio of 1:1, while the Mn enzyme ratio was 2:1. The Mn enzyme was slightly less stable. It would be interesting to extend these studies to other organisms. The Fe superoxide dismutase from *Bacteroides fragilis* has been reconstituted as an Mn-containing enzyme.[1359]

Little is known about the mechanism of superoxide disproportionation in these cases, except that it appears to be different from that of the Cu/Zn enzyme. There also appear to be some differences between the Mn and Fe enzymes.

62.1.12.9 Peroxidases and Catalases

These are hemoprotein enzymes that catalyze the reactions of hydrogen peroxide in animals and plants. Peroxidase catalyzes the oxidation of a wide range of compounds by hydrogen peroxide, while catalase catalyzes the disproportionation of hydrogen peroxide (equations 69 and 70). There are a number of similarities between the two groups of enzymes, one of them being the occurrence of high oxidation state intermediates during the cycle. Catalases and peroxidases from plant sources all contain the prosthetic group ferriprotoporphyrin IX.

$$H_2O_2 + SH_2 \xrightarrow{\text{peroxidase}} 2H_2O + S \quad (69)$$

$$H_2O_2 + H_2O_2 \xrightarrow{\text{catalase}} 2H_2O + O_2 \quad (70)$$

62.1.12.9.1 Peroxidase[1360–1362]

Several peroxidases will be considered in this section, but most studied is horseradish peroxidase (HRP), which is present in high concentration in the root of the horseradish plant. Others of

interest are cytochrome *c* peroxidase, chloroperoxidase, myeloperoxidase, lactoperoxidase, thyroidperoxidase and glutathione peroxidase. Glutathione peroxidase is a non-heme peroxidase that contains-selenium.

Horseradish peroxidase (HRP) contains a polypeptide of molecular weight 33 890 (from sequence measurements), some carbohydrate and the protoporphyrin IX. Two calcium ions are also present, probably for the stabilization of protein conformation. The fifth coordination position of the Fe^{III} in native HRP is filled by an imidazole group, while the sixth may be vacant. In solutions of low pH, HRP is high-spin, but there is a change to low-spin at high pH, with a pK_a value for the equilibrium between the two forms of about 11. The alkaline form may result from the coordination of an additional nitrogen ligand in the sixth position, although rate constants for the reverse reaction (the conversion of the alkaline species to the neutral species) seem too fast for a ligand displacement reaction.

The treatment of peroxidases in the Fe^{III} resting form with hydrogen peroxide gives a green species (for HRP) known as compound I, which is oxidized to a level of two equivalents above Fe^{III}. On slow decomposition, compound I is converted into a red product, compound II, which has one oxidizing equivalent above Fe^{III}. In the presence of a substrate, compound I is reduced to compound II, and then compound II is reduced to the native enzyme (equations 71–73, where AH is a reducing substrate, and A· the radical product which will react further). In some cases oxidation of substrate is a direct two electron process.

$$P + H_2O_2 \rightarrow \text{compound I} + H_2O \quad (71)$$

$$\text{compound I} + AH \rightarrow \text{compound II} + A\cdot \quad (72)$$

$$\text{compound II} + AH \rightarrow P + A\cdot \quad (73)$$

It appears that both HRPI and HRPII contain Fe^{IV}, as their Mössbauer spectra are very similar. The additional oxidizing equivalent in HRPI exists as the porphyrin π-cation radical, as shown by the use of ENDOR techniques.[1363] The observation of ^{17}O ENDOR from HRPI prepared with $H_2{}^{17}O_2$ proves that one oxygen atom from the peroxidase remains with the intermediate, and that an oxidizing equivalent is associated with an oxoferryl centre.[1364] Detailed analysis suggests a triplet oxoferryl group ($Fe^{IV}{=}O$) whose axis lies normal to the porphyrin cation plane, with the two unpaired electrons substantially delocalized between the two atoms through d_π–p_π bonding. There is similarity between the optical spectra of HRPI and synthetic porphyrin π-cation complexes. Magnetic susceptibility measurements suggest an $S = \frac{3}{2}$ ground state for HRPI, consistent with a ferromagnetically coupled low-spin Fe^{IV} and the porphyrin π-cation ($S = \frac{1}{2}$).

EXAFS measurements on HRPI and HRPII, compared with highly oxidized synthetic iron porphyrins, are consistent with Fe^{IV} formulations, and confirm the Fe^{IV}-porphyrin π-cation structure for HRPI. The presence of a short Fe—O bond has been confirmed.[1365] Resonance Raman measurements have allowed the assignment of the Fe—histidine stretching frequency in HRP (279 cm^{-1}), HRPI (248 cm^{-1}) and HRPII (287 cm^{-1}).[1366] This suggests that changes in charge distribution of the Fe—histidine bond occur, and may be involved in the activation of the *trans* oxygen atom.

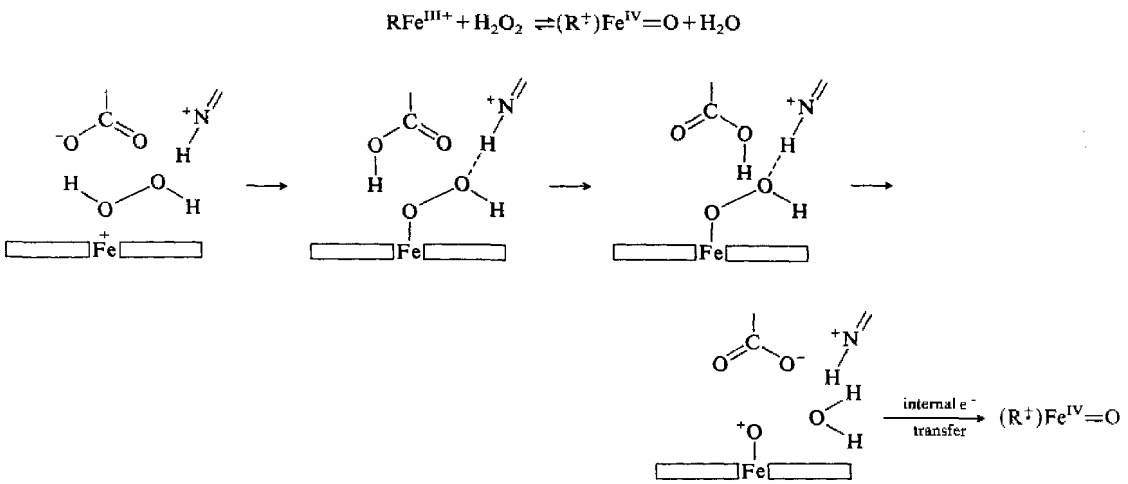


Figure 63 Mechanism of formation of compound I in peroxidase

The formation of compound I is thought to depend upon aspartate-43 and arginine-38, as detailed in the mechanism shown in Figure 63.[1362] Two-electron oxidations of substrate may occur by oxygen atom transfer, but formation of compound II could proceed by reaction (74).

$$(R^{+})Fe^{IV}{=}O + SH \rightarrow Fe^{IV}{=}\dot{O}H + S\cdot \qquad (74)$$

In addition to compounds I and II, there is also compound III, formed by reaction of the iron(II) peroxidase with dioxygen. This is analogous to oxymyoglobin, and so is superoxide-iron(III) peroxidase. The similarity between metmyoglobin and peroxidase should be stressed. They have the same prosthetic group and axial ligand, and appear to differ in coordination number only. Thus metmyoglobin gives a compound II-like product on reaction with hydrogen peroxide, although the reaction is slower, as water has to be displaced and the appropriate distal catalytic groups are absent.

62.1.12.9.2 Cytochrome c peroxidase

This is usually isolated from yeast, and has a molecular weight of 53 000 with one heme *b*. It catalyzes the oxidation of ferrocytochrome *c* by hydrogen peroxide. It is the first peroxidase for which the structure has been determined.[1367] The imidazole axial ligand is His-174, while Arg-48, Trp-51 and His-52 provide distal catalytic groups. The mechanism involves nucleophilic attack of peroxide on the Fe^{III}, loss of the ROOH proton to the imidazole of His-52, and transfer of this proton to the leaving RO^{-} group. Compound I of cytochrome *c* peroxidase is red, and differs from HRPI in that the additional oxidizing equivalent is on a protein residue. ESR and ENDOR spectra have been interpreted in terms of a methionine-centred free radical.[1368] One possibility is that a ferryl porphyrin cation radical is formed with cytochrome *c* peroxidase (it is attractive to assume that this would be common to all peroxidases), but that cytochrome *c* peroxidase has a readily oxidizable substrate which reduces the porphyrin radical.[1369]

Cytochrome *c* peroxidase may also be isolated from *Pseudomonas* spp. and differs from the yeast enzyme described above. *Pseudomonas* cytochrome *c* peroxidase contains two covalently bound heme *c* moieties in a single polypeptide chain, of molecular weight 50 000. The enzyme from *Ps. denitrificans* has a molecular weight of 63 000 with two heme *c* groups.[1370]

There is good evidence to show that the two hemes in *Pseudomonas* cytochrome *c* peroxidase are not equivalent. One is a *c* type heme (+320 mV), and the other is a *c'* heme (−330 mV) and is a peroxidatic group. A number of techniques, including CD, absorption and resonance Raman spectroscopy,[1371,1372] show that the fifth ligand in both hemes is an imidazole group. In the oxidized enzyme, the high-potential heme is low-spin with methionine as the sixth ligand. On reduction, the sixth ligand changes to imidazole or lysine. The low-potential heme is high-spin, six-coordinate with water as an axial ligand when oxidized, and five-coordinate when reduced.

Kinetic studies have shown that the product formed in the reaction of the fully oxidized enzyme with hydrogen peroxide is catalytically inactive. Reaction of the half-reduced enzyme with hydrogen peroxide leads to an enzymatically active compound, in which the Fe^{II} heme is oxidized to Fe^{III}, and the Fe^{III} heme is oxidized to the Fe^{IV} ferryl species. No stoichiometric formation of a radical species is observed, unlike the case for other peroxidases. The peroxide-oxidized enzyme will then oxidize two molecules of reduced cytochrome *c*. Mechanistic details are still unclear, particularly with regard to the interaction between the two heme groups, a phenomenon revealed by ESR studies.[1373]

62.1.12.9.3 Chloroperoxidase

This may be isolated from *Caldariomyces fumago*. It catalyzes the oxidation of chloride ions in the halogenation of a large group of substrates, and will also catalyze the peroxidation of organic compounds. The latter reaction involves the formation of compound I, and two subsequent one-electron reductions to give compound II and the native enzyme. The halogenation reaction may involve an intermediate halogenium species, although these intermediates are very unstable. A vanadium-containing bromoperoxide has been isolated from a seaweed, *Ascophyllum nodosum*.[1566]

62.1.12.9.4 Myeloperoxidase

This is present in neutrophils, and catalyzes the production of hypochlorite from hydrogen peroxide and chloride. The hypochlorite then reacts with superoxide to generate hydroxyl radical

and/or $^1O_2$ (equations 75 and 76). These reactive species may be used in attack on bacteria. The α-1-proteinase inhibitor is inhibited by myeloperoxidase in the presence of chloride and peroxide, due apparently to the oxidation of a methionine residue to a sulfoxide. The enhanced proteolytic activity of neutrophils may be due to this reaction.[1374]

$$H_2O_2 + Cl^- \xrightarrow{MPO} HOCl + HO^- \quad (75)$$

$$HOCl + O_2^- \rightarrow OH\cdot + O_2 + Cl^- \quad (76)$$

62.1.12.9.5 Glutathione peroxidase

Glutathione peroxidase is not a hemoprotein, but contains selenium, present as selenocysteine in the protein backbone.[1375] It catalyzes the reduction of a large range of lipid hydroperoxidases and hydrogen peroxide,[1376] the former reaction representing an important defence against damage to biological membranes. The structure has been determined to 2.8 Å resolution.[1375] It is a tetramer with molecular weight 84 000 and one selenium per subunit. The selenium undergoes a reversible substrate-induced redox change. This may be a two-electron cycle between a selenic acid (RSeOH) and a seleninic acid (RSe(O)OH).

62.1.12.9.6 Catalase

The major function of catalase is the decomposition of peroxides, but it can also act as a peroxidase. Catalases usually have molecular weights of about 240 000, with four identical subunits. Each subunit contains protoporphyrin IX, with high-spin Fe^{III}, and an amino acid residue in the axial position. The mechanism of action of catalase involves the oxidation by H_2O_2 of the Fe^{III} catalase to compound I, two equivalents higher in redox state, and its subsequent reduction *via* compound II. Compound II may be oxidized by hydrogen peroxide to give compound III, which appears to have three oxidizing equivalents above Fe^{III}.

Catalase isolated from *Neurospora crassa*[1377] differs from other catalases in having a rather higher molecular weight (320 000) and a novel heme group, suggested to be a dihydroporphyrin complex with high-spin iron(III). The inactivation of nitrite reductase in *N. crassa* occurs through the formation of H_2O_2. So the physiological role of the *N. crassa* catalase may be to provide protection for nitrite reductase against inactivation by peroxide.

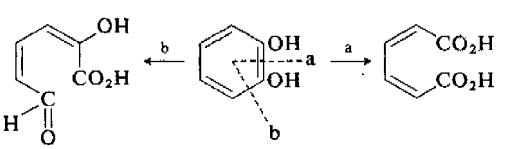
Other microorganisms which are unable to synthesize heme produce a catalase which is evidently not a heme catalase as it is not subject to inhibition by cyanide or azide. This pseudocatalase of *Lactobacillus plantarum* contains manganese.[1378] The enzyme is pink in concentrated solution, and has a molecular weight of 172 000 ± 4000, with six non-covalently associated subunits, each containing one Mn^{II} in the resting enzyme. The functional role of the pseudocatalase is confirmed by studies on various strains of *L. plantarum*. Strains which contain the manganese catalase do not accumulate hydrogen peroxide in the growth medium. A possible mechanism could involve oxidation of Mn^{II} to Mn^{V} by hydrogen peroxide, the Mn^{V} then oxidizing a second molecule of hydrogen peroxide.

62.1.12.10 Dioxygenases

The metal-containing dioxygenases usually contain iron, either as a heme group or, more usually, as non-heme iron.

62.1.12.10.1 Non-heme dioxygenases

Dioxygenases which act on aromatic *ortho*-diphenols may either cleave the aromatic ring by an intradiol pathway or by an extradiol route, as shown in equation (77).



(77)

Intradiol dioxygenases are typified by catechol 1,2-dioxygenase[1379,1380] and protocatechuate 3,4-dioxygenase. These are red proteins, having a visible absorption at 460 nm, assigned to charge transfer between a tyrosine ligand and iron(III). The extradiol proteins are different in several respects, including spectra. Thus they are colourless and ESR-silent.

Catechol 1,2-dioxygenase catalyzes the intradiol cleavage of catechol by dioxygen, with both oxygen atoms incorporated into the product *cis,cis*-muconic acid. Protocatechuate 3,4-dioxygenase has been purified from several bacteria, and varies in subunit composition from species to species. Both enzymes under discussion involve mononuclear Fe^{III} centres. X-Ray absorption spectroscopy[1381] on the catechol 1,2-dioxygenases and other iron-tyrosinate proteins (the transferrins and the purple acid phosphatases), together with EXAFS[1382] and resonance Raman data have led to the postulate of a model for the dioxygenase active site with six-coordinate iron(III) having two histidine and two *cis*-tyrosine ligands, together with an aqua group and a sixth unidentified ligand X which is easily dissociated. Loss of the ligand X gives a five-coordinate complex with an apical and a basal tyrosine. This would account for the occurrence of Fe-tyrosine charge-transfer bands of different energy.

Binding of the catechol to the enzyme occurs before interaction with dioxygen. So the enzyme-substrate complex can be observed under anaerobic conditions. The ESR spectra of these complexes show the iron to be high-spin Fe^{III} with axial distortions. Resonance Raman studies show that the catechol is coordinated to the iron, probably in a monodentate mode, as indicated by NMR spectroscopy.[1383]

On exposure to dioxygen, the enzyme-substrate complex reacts to give the product *via* two intermediates.[1384] The first resembles ESO_2, and the second a steady state intermediate. The intermediate ESO_2 remains a high-spin Fe^{III} complex. No evidence has been found for the involvement of Fe^{II} in the catalytic pathway, for example by reduction of Fe^{III} by the catechol substrate. The type of activation mechanism discussed for other enzymes cannot therefore hold. A mechanism suggested by Que and his coworkers is shown in Figure 64. In this scheme, the substrate binds as monodentate ligand and loses both protons. This binary complex transfers one electron to dioxygen, giving an Fe^{III}-semiquinone-superoxide species. The two radicals couple to give the hydroperoxide, which then decomposes to product. Interaction of the dioxygen with Fe^{III} is eliminated by the failure to observe $\nu(O_2)$ bands in the resonance Raman spectrum of the intermediate.

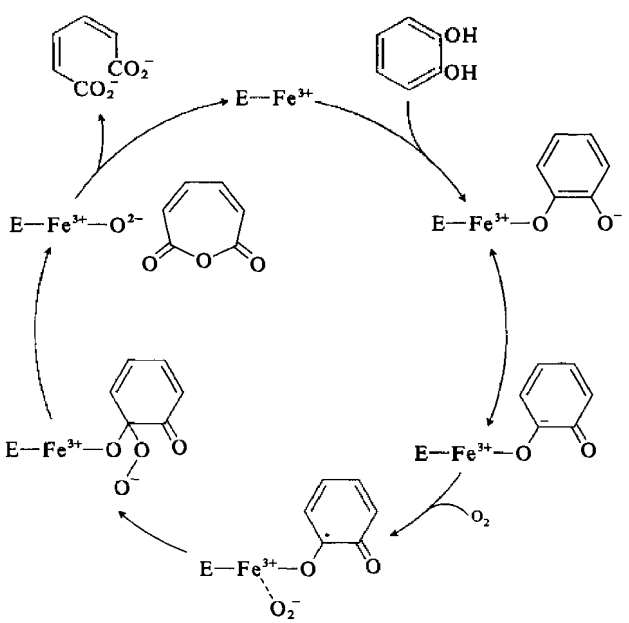


Figure 64 Possible mechanism for the intradiol dioxygenases

The extradiol dioxygenases are more common than the intradiol enzymes, and are more diverse in their reactions.[1379] Examples are catechol 2,3-dioxygenase (from *Pseudomonas arvilla* and *Ps. putida*) and protocatechuate 4,5-dioxygenase from *Ps. testosteroni*. These are colourless and

ESR-silent, suggesting low-spin Fe^{II}. This has been confirmed by the use of Mössbauer spectroscopy. Kinetic studies suggest that a substrate-enzyme complex is formed before interaction with dioxygen. Binding of substrate has no effect upon the Mössbauer spectrum, so it is not certain that it binds to the Fe^{II} centre.

Other non-heme dioxygenases include the lipooxygenases and a group of apparently related iron–sulfur proteins. This group is made up of the toluene and benzene dioxygenases from *Ps. putida*, the benzoate 1,2-dioxygenase from *Ps. arvilla* and pyrazon dioxygenase from pyrazon-degrading bacteria. Pyrazon is the active ingredient in the herbicide Pyramin. Bacterial degradation of pyrazon is initiated by the oxidation of its phenyl moiety to the corresponding *cis-ortho*-dihydrodihydroxy compound, as shown in equation (78). The benzene dioxygenase[1385] converts benzene into *cis*-benzene glycol in the presence of NADH, O_2 and Fe^{2+}. It is a multienzyme complex of three components, a flavoprotein, an intermediate electron transfer iron–sulfur protein and a terminal dioxygenase. The terminal dioxygenase has a molecular weight of 215 300 and contains two [2Fe–2S] centres, as demonstrated by cluster extrusion experiments and by Mössbauer spectroscopy. The dioxygenase binds dioxygen and substrate. The requirement for additional Fe^{2+} has been interpreted in terms of a site for activation of dioxygen on $[2Fe\text{–}2S]Fe^{2+}$, as proposed initially for 4-methoxybenzoate monooxygenase.[1386]

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+ \quad (78)$$

The toluene dioxygenase,[1387] benzoate 1,2-dioxygenase[1388] and pyrazon dioxygenase[1389] all contain [2Fe–2S] clusters and require Fe^{2+}, although the stoichiometries differ as shown in Table 28. It appears very probable that they all contain the $[2Fe\text{–}2S]Fe^{2+}$ site for activation of dioxygen.

Table 28 Some Non-heme Dioxygenases

Enzyme	*MW of dioxygenase*	*Clusters*	*Fe^{2+}*
Benzene dioxygenase (*Pseudomonas putida*)	215 000	2 [2Fe–2S]	$2Fe^{2+}$
Toluene dioxygenase (*Ps. putida*)	151 000	[2Fe–2S]	Needs Fe^{2+}
Pyrazon dioxygenase (pyrazon-degrading bacteria)	180 000	[2Fe–2S]	?
Benzoate 1,2-dioxygenase (*Ps. arvilla* C-1)	201 000	3 [2Fe–2S]	$3Fe^{2+}$

62.1.12.10.2 Heme dioxygenases

This group is illustrated by tryptophan 2,3-dioxygenase and indolamine 2,3-dioxygenase, which catalyze the insertion of molecular oxygen into the pyrrole ring of tryptophan derivatives. In these

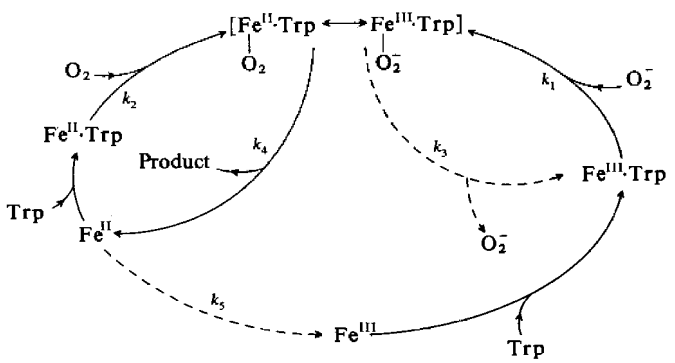


Figure 65 Catalytic cycles of indolamine dioxygenase (reproduced with permission from *J. Biol. Chem.*, 1979, **254**, 3288)

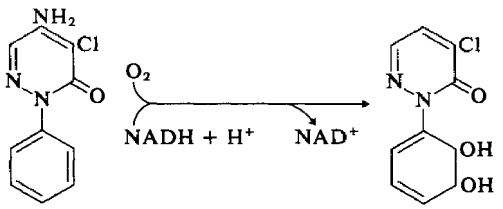
cases there is good evidence for reduction of the metal to Fe^{II} before dioxygen is bound, and that activation of the dioxygen involves electron transfer from the metal to the bound dioxygen, to give an Fe^{III} superoxide complex. Maximum activity of the enzyme results from the presence of superoxide-generating systems, when the Fe^{III} superoxide complex can be formed directly.[1390] The Fe^{II} enzyme binds tryptophan, and then O_2. The Fe^{III} enzyme binds superoxide first and then tryptophan. An assessment of these steps is given in Figure 65.

62.1.12.11 Monooxygenases

Several diverse metal centres are involved in the catalysis of monooxygenation or hydroxylation reactions. The most important of these is cytochrome P-450, a hemoprotein with a cysteine residue as an axial ligand. Tyrosinase involves a coupled binuclear copper site, while dopamine β-hydroxylase is also a copper protein but probably involves four binuclear copper sites, which are different from the tyrosinase sites. Putidamonooxin involves an iron–sulfur protein and a non-heme iron. In all cases a peroxo complex appears to be the active species.

62.1.12.11.1 Cytochrome P-450

Cytochrome P-450 is a hemoprotein that is distributed widely in nature in animal tissue and organelles, and in plants and microoganisms. Its main function lies in the monooxygenation of lipophilic substances, in which two electrons are taken up from NADPH with the reduction of one atom of dioxygen to water and insertion of the other into the substrate (equation 79).



(79)

A wide variety of reactions are catalyzed by cytochrome P-450. These are described well in recent reviews[1391,1392] and in the proceedings of a recent symposium.[1393] In addition to contributing to metabolically important reactions, cytochrome P-450 is also involved in catalyzing reactions of xenobiotics, usually to lead to detoxification, but sometimes to give even more toxic products.[1394,1395]

Cytochrome P-450 is named from the optical spectrum of its reduced complex with carbon monoxide, which has a maximum absorption at 450 nm, an unusually long wavelength. Most studies have been carried out with liver microsomal cytochrome P-450. The active site contains an iron protoporphyrin IX in a hydrophobic cleft in the surface of the protein. The heme is bound to the protein through the axial ligand, which is a cysteine residue. The sixth ligand in the resting enzyme is probably water. On reduction to Fe^{II} this sixth position is the site of activation of dioxygen. Ligands such as carbon monoxide or nitric oxide will also bind at this site. Interest in the reactivity of cytochrome P-450 has prompted a great deal of work on model iron porphyrin complexes with a thiolate axial ligand.[1392,1396,1397]

A catalytic cycle for cytochrome P-450 is shown in Figure 66. It is initiated by binding of the substrate to the native, low-spin iron(III) enzyme, *via* a hydrophobic guest–host interaction, to give a high-spin iron(III) species. Reduction to the iron(II) state by electron transfer (from flavoprotein or the iron–sulfur protein putidaredoxin) is followed by binding of O_2 to give a diamagnetic oxy compound, similar to oxyhemoglobin. The presence of the axial sulfur ligand facilitates electron transfer from Fe^{II} to give an $Fe^{III}(O_2^-)$ species. This is probably reflected in the ease with which the P-450 oxy adduct dissociates into Fe^{III} P-450 and superoxide compared to myoglobin.

Addition of a second electron to the superoxo species is followed by cleavage of the O—O bond, with one oxygen atom being lost as water. The other oxygen atom is inserted into the C—H bond of the substrate to give the corresponding alcohol, which is then released to complete the catalytic cycle.

The most unclear part of this cycle is the mechanism of cleavage of the O—O bond. Transfer of the second electron leads formally to the presence of a peroxo group bound to Fe^{III}, but the actual electronic distribution is not known. It seems unlikely that the $Fe^{III}(O_2^{2-})$ group would be

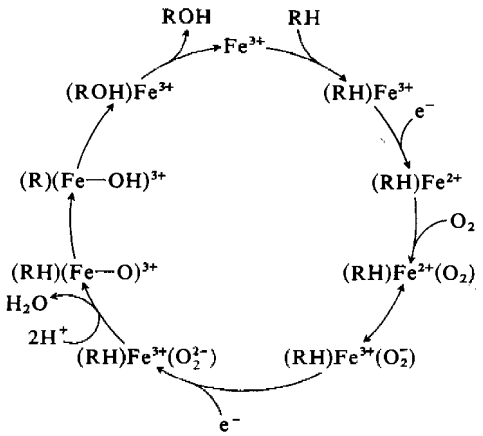


Figure 66 Scheme for the mechanism of action of cytochrome P-450 in hydroxylation reactions (reproduced with permission from *Annu. Rev. Biochem.*, 1980, 4)

reactive towards alkanes. Two general pathways are usually considered: one involves homolytic cleavage of the peroxide, while the other (the oxenoid pathway) involves heterolytic cleavage. Both routes involve acylation of the iron(III)-bound peroxide, and differ in the subsequent lysis step, leaving formally either hydroxyl radical or an oxygen atom bound to the metal. In the first case the liberated hydroxyl radical abstracts a hydrogen atom from a nearby group producing water. It should also be noted that the thiolate axial ligand can participate in electron-redistribution reactions within these species. The two pathways are outlined below (equations 80 and 81). In these schemes iron is represented as Fe^{III} for convenience, but the first product of O—O fission in the oxenoid pathway could be a perferryl complex $Fe^{V}(O^{2-})$, or porphyrin radical cations could be formed as in $Fe^{IV}(O^{2-})P^{+}$. In the oxenoid pathway, the bound oxygen radical abstracts hydrogen from the substrate to give a bound hydroxyl radical, which recombines with the substrate radical to give the product. In the homolytic pathway, it is assumed that the substrate is converted to a radical species by loss of a hydrogen atom to the free radical group generated earlier, and then combines with the bound hydroxyl radical.

$$\text{Oxenoid: } -S^- Fe^{III}O \rightarrow -S\cdot Fe^{III}O^- \xrightarrow{RH} -S\cdot Fe^{III}OH^- + R\cdot \rightarrow -S^- Fe^{III} + ROH \quad (80)$$

$$\text{Homolysis: } -S^- Fe^{III}OH \rightarrow -S\cdot Fe^{III}OH^- \xrightarrow{R\cdot} -S^- Fe^{III} + ROH \quad (81)$$

Alkyl hydroperoxides support the cytochrome P-450 oxidation of substrates, confirming the key role for peroxide intermediates. In general the homolysis pathway is then favoured, but the oxenoid mechanism is possible in reactions involving oxygen donors such as periodate and iodosylbenzene where the homolytic pathway seems unlikely. In the case of iodosylbenzene as oxygen donor, solvent oxygen atoms became incorporated into the product, confirming the intermediacy of the $Fe^{5+}=O$ species, which can exchange oxygen with water. Unactivated alkanes are hydroxylated catalytically[1398] by iodosylbenzene and various iron porphyrins. The data,

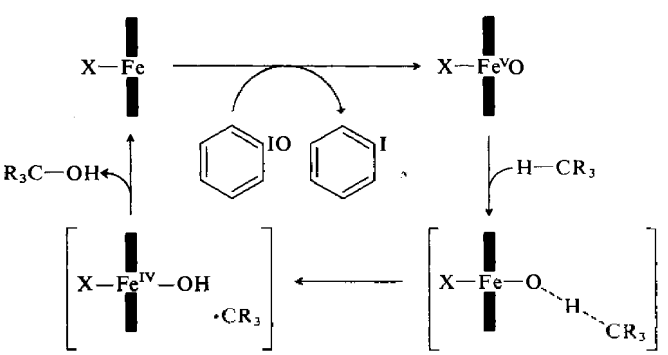


Figure 67 Hydroxylation of alkanes by iodosylbenzene and iron porphyrins

including deuterium isotope effects, are consistent with the free radical scheme suggested earlier for P-450. In this case the reactive oxygen species is the iron(IV) porphyrin cation radical, $Fe^{IV}(O^{2-})P^{+}$. The scheme is shown in Figure 67.

62.1.12.11.2 Tyrosinase

This protein contains a coupled binuclear copper site that appears to be very similar to that found in hemocyanin (Section 62.1.12.3.8).[1399] Tyrosinase catalyzes the hydroxylation of monophenols, and also behaves as an oxidase in the oxidation of *ortho*-diphenols. The deoxy protein [copper(I)] binds dioxygen to give oxytyrosinase, which is a Cu^{II} peroxide species with antiferromagnetic coupling between the two Cu^{II} centres. The oxybinuclear site is diamagnetic to the most sensitive detectors.[III]

Photooxidation studies have implicated His-188, His-192, His-289 and either His-305 or His-306 as ligands to copper. The structure of the active site is shown in Figure 68. The pair of Cu^{II} centres may be replaced by two Co^{II} centres, but an oxy derivative cannot be prepared.[1400] It appears probable that the oxytyrosinase is the hydroxylating species.

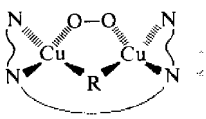


Figure 68 Model for the active site in tyrosinase

62.1.12.11.3 Dopamine β-hydroxylase

This is a tetrameric copper-containing glycoprotein, which catalyzes the conversion of dopamine into norepinephrine, a hormone/neurotransmitter, and also the hydroxylation of a number of substituted phenylethylamines.[1401–1403] Consideration of this enzyme has been hindered by uncertainty over the stoichiometry of binding of copper, and, until recently, there seemed to be good evidence for four copper ions per molecule.[1404] However, there is now convincing support for a stoichiometry of eight copper ions per molecule, with two per subunit.[1405,1406] This conclusion is based upon analysis and titration methods.

Both copper centres in each subunit appear to be essential for catalytic activity, and cannot be replaced by other metal ions. Two electrons are involved in the redox reaction to give norepinephrine, and it seems reasonable to postulate a bridging site between two Cu^{I} centres for dioxygen, with production of peroxide and Cu^{II}. However, the copper centres in each subunit are ESR detectable,[1404] and may not, therefore, present a type 3 site. In this case dioxygen must coordinate to one copper(I) centre, with electron transfer from the second copper(I) centre.

62.1.12.11.4 Putidamonoxin

This is the oxygenase of a 4-methoxybenzoate monooxygenase enzyme. It is made up of three subunits, and contains [2Fe-2S] chromophores and one mononuclear non-heme iron as cofactor,[1386] similar to the situation described for the non-heme dioxygenases. The monooxygenase in its oxidized state forms an enzyme-substrate complex, which is then reduced by the transfer of two electrons from the reductase. Dioxygen binds to the reduced enzyme and is activated by transfer of two electrons from the reduced [2Fe-2S] cluster and one electron from the mononuclear Fe^{2+}. The mononuclear non-heme iron appears to be five-coordinate in its reduced form, the sixth position probably providing the binding site for molecular oxygen. The bound peroxide then hydroxylates the substrate, with the formation of water.

62.1.13 ELECTRON-TRANSFER REACTIONS

In the preceding sections, consideration has been given to important classes of metalloproteins which are involved in electron transfer, namely cytochromes, iron–sulfur proteins and the blue

copper proteins. These are associated with electron transfer in respiration and photosynthesis, and in a number of complex enzymatic processes such as nitrogen fixation. In addition, the flavoproteins[1407] should also be included although outside the scope of this chapter. All four classes of electron-transfer proteins have structures which have a minimum amount of structural change during electron transfer.

The fine tuning of redox potential is important for the correct functioning of these metalloproteins. An attempt has been made to indicate the way in which this occurs through the heme and/or protein moieties. Finally, it should be noted that electrons are often transferred over considerable distances from one redox centre to another, although this phenomenon is not at all well understood. This too will be reflected in the role of the protein and heme ligand groups, with mobile, highly conjugated electronic systems. A number of general reviews on electron transfer in chemistry and biology are available.[1407–1419] The following discussion draws attention to salient features without presenting a detailed analysis.

62.1.13.1 Types of Electron-transfer Reaction

A number of situations may be visualized. Electron transfer may take place between a pair of redox proteins in solution. Certain reactions in the cytoplasm of the red blood cell fall into this category, such as that between hemoglobin and cytochrome *b* reductase. These reactions will probably occur by an outer-sphere mechanism, as was described earlier for model reactions between isolated electron-transfer proteins and also between these proteins and simple complexes. Interaction between such proteins probably utilizes specific charged areas on their surfaces. The possibility of inner-sphere reactions may have to be considered in a few cases.

Electron transfer in respiration involves a chain of (usually) membrane-bound proteins arranged in a highly organized way for greater efficiency and control. The distances between the redox centres may well be greater and the question of electron transfer over long distances may be of greater significance than is the case for reactions in solution.

Finally, intramolecular electron transport occurs in multicentre redox proteins, and represents a rather different situation.

In all cases there is a need for the rapid transfer of electrons in a controlled direction. It is to be expected that ligands will have mobile, conjugated electronic systems to allow electrons to be transported away rapidly from the metal centre to avoid recombination with the positive hole. In addition to movement of electrons through the binding system, the possibility of electron tunnelling must be considered.

62.1.13.2 Requirements for Fast Electron Transfer

A number of now well-known requirements have to be satisfied before rapid electron transfer occurs.

As indicated by the Franck–Condon principle, electron transfer does not occur until the metal centre is vibrationally excited to a geometry appropriate for that of the product complex formed in the redox reaction. The necessary reorganization of the metal site thus represents an additional contribution to the activation energy of the reaction. It follows, therefore, that electron transfer will be fast when this structural reorganization is minimal. In the blue copper electron-transfer proteins, this situation is controlled by the protein in that it enforces a geometry on the copper that is intermediate between that preferred by Cu^{I} and Cu^{II}. The ability of the protein to enforce a geometry on the metal that is appropriate for its transition state during reaction is embodied in the entatic state hypothesis.[1420] In general a flexible arrangement around the active site to allow small changes in structure in a particular direction may be essential.

The ligand should be polarizable, as noted earlier, and also to allow the electronic charge to be delocalized, with smaller bond length changes occurring on redox change. Easier transfer of charge to the ligand, *via* d_{π}–p_{π} bonding, will take place if the ligand is high in the nephelauxetic series. This will allow the *d*-orbitals to expand outwards and overlap more effectively. If the ligand is a large ligand then this will result in facilitated transfer of the electron over a long distance. The porphyrin fulfils many of these requirements effectively.

Electron transfer will occur more easily if the metal ion is in the low-spin configuration, as the electron density will then lie in orbitals directed towards the ligand. Changes of spin state during reaction should be avoided, while reactions should be complementary if possible.

Finally, it is now clear that electron transfer between metal centres occurs readily when there are small differences in redox potential. Reactions which are considerably exothermic may be slower than expected due to difficulty in dissipating the energy released.[1409,1421]

62.1.13.3 Intramolecular, Long-distance Electron Transfer

Relatively rapid electron transfer can occur between metal centres in proteins which are separated by distances of over 10 Å. One example is the hybrid hemoglobin in which two chains of one type are substituted with a Zn^{II} protoporphyrin while the two chains of the other type contain an aquairon(III) heme.[1422] In the configuration adopted by the deoxy hybrid hemoglobin, the two closest prosthetic groups will be the zinc and iron porphyrins, which will have roughly parallel porphyrin planes with a metal–metal distance of 25 Å, and a 20 Å gap between porphyrin atoms. Electron transfer between the two centres may be initiated by flash photoexcitation which gives the long-lived ^{3}Zn porphyrin excited state. This species will undergo decay, but is able to reduce the Fe^{III} centre, as is demonstrated by a doubling of the decay rate of the triplet state to give $k_{obs} = 140 \pm 20\ s^{-1}$, and the electron transfer rate constant $k_t = 60 \pm 25\ s^{-1}$. This reaction produces the $(ZnP)^+\pi$-cation radical, which then rapidly oxidizes the Fe^{II} porphyrin, with k greater than $10^2\ s^{-1}$ and probably equal to $10^3\ s^{-1}$. The latter reaction is less exothermic than the original reaction but is faster, as noted in Section 62.1.13.1.1.

Most other studies have been concerned with intramolecular electron transfer between a native metal in a protein and a pentaammineruthenium centre attached to a peripheral histidine residue in the protein. Examples are azurin, labelled at His-83,[1423] and cytochrome *c*, labelled at His-33.[1424] Electron transfer in the first case occurs between the imidazole of His-83 and the sulfur of Cys-112 and involves a distance of 11.8 Å. The reaction is initiated by flash photolysis techniques to give $(NH_3)_5Ru\text{-}His\text{-}83^{2+}\cdots Az(Cu^{2+})$. Electron transfer between Ru and Cu occurs with a rate constant of $k = 1.9\ s^{-1}$ and is independent of temperature. This confirms that reorganization enthalpy is minimal. In the reaction with labelled cytochrome *c*, electron transfer occurs over 15 Å with $k = 25\ s^{-1}$, and is independent of temperature. Again, the lower rate constant is found for the reaction with the highest driving force. It has been noted that electron transfer in the $(NH_3)_5Ru\cdots$azurin case involves twice as many peptide bonds between the two metal centres as there are in the $(NH_3)_5Ru\cdots$cytochrome example, suggesting that the difference in rate constant may reflect the possibility of a through-bond pathway rather than a through-space route. However, it will be necessary for more studies on electron transfer between crystallographically defined sites before a conclusion can be drawn. Rates of electron transfer through bridges will fall as the distance to be travelled is increased.[1425] Such electron transfer may involve σ- and π-components,[1426] but activation energies for such processes may be higher than that found for biological electron transport.

The establishment of fast electron transfer over these distances of up to 25 Å is important, as similar distances are involved in certain natural redox partners. Thus cytochrome *c* and cytochrome *c* peroxidase form a complex in which the heme edge-to-edge separation is about 16 Å.

Amino acid side-chains may have a role in electron transfer in proteins through the well-known 'hopping pathway'. In this process electrons could move between certain residues such as tyrosine and tryptophan, with the generation of free radical intermediates. Such free radical residues are known in certain high oxidation state species of hemoproteins.

62.1.13.4 Electron-transfer Chains

The electron-transfer centres in electron-transfer chains are usually but not always membrane bound, and so present considerable difficulties in purification, particularly from excess phospholipid. These proteins may span the membrane or be embedded from one side only. Other proteins may bind to surface components of the membrane and be separated more readily.

The frequent association of electron-transfer proteins with membranes reflects the important role of the membrane in controlling the orientation of the proteins for fast electron transfer. It ensues that electron transfer utilizes all the redox components and does not bypass electron-transfer proteins having associated essential functions such as proton pumping. The existence of such gradients associated with electron transfer would not be possible in the absence of the membrane.

Electrons will enter the electron-transfer chain at a suitable potential appropriate for the chemical reaction from which they originate. They will run downhill thermodynamically to the

reducible electron acceptor, *via* a large number of redox centres which have small differences in redox potential (~80 mV). The presence of a large number of redox centres means that the distance between redox centres is decreased, while the small differences in redox potential allow partial reversibility.

62.1.13.4.1 The coupling of electron transfer to the synthesis of ATP

The transfer of electrons in respiratory and photosynthetic electron-transfer chains is linked by protons to the synthesis of ATP from ADP and inorganic phosphate. Certain components of the chain, such as cytochrome oxidase, act as proton pumps so that an electrochemical proton gradient is set up across the membrane in response to the transfer of electrons. Return of protons across the membrane down the gradient can then drive the synthesis of ATP. Such a proton electrochemical gradient $\Delta\mu_{H^+}$ or protonmotive force has two components, a membrane potential $\Delta\psi$ and a pH gradient ΔpH. This coupling of electron transfer to ATP synthesis by protons is described in the chemiosmotic theory[1427] of Mitchell,[1428–1430] although an alternative 'local proton' viewpoint has been proposed simultaneously.[1431,1432] Many aspects of these proton electrochemical gradients and energy transduction processes have been considered.[1433,1434]

62.1.13.4.2 Electron transfer in mitochondria

The components of the electron-transfer chain in mitochondria are shown in Figure 69. The sites at which ATP is synthesized are noted. The cytochromes may be characterized by UV-vis studies on membranes, usually by difference spectra. The iron-sulfur proteins may be identified by ESR spectroscopy, but MCD may be of particular value in characterizing isolated clusters.

Interesting results have been obtained for mitochondrial particles prepared from the yeast *Candida utilis* grown in a medium containing ^{57}Fe. This allowed hyperfine interactions for ^{57}Fe atoms in the ESR spectrum to be characterized. Certain of the iron-sulfur proteins are also proton pumps.

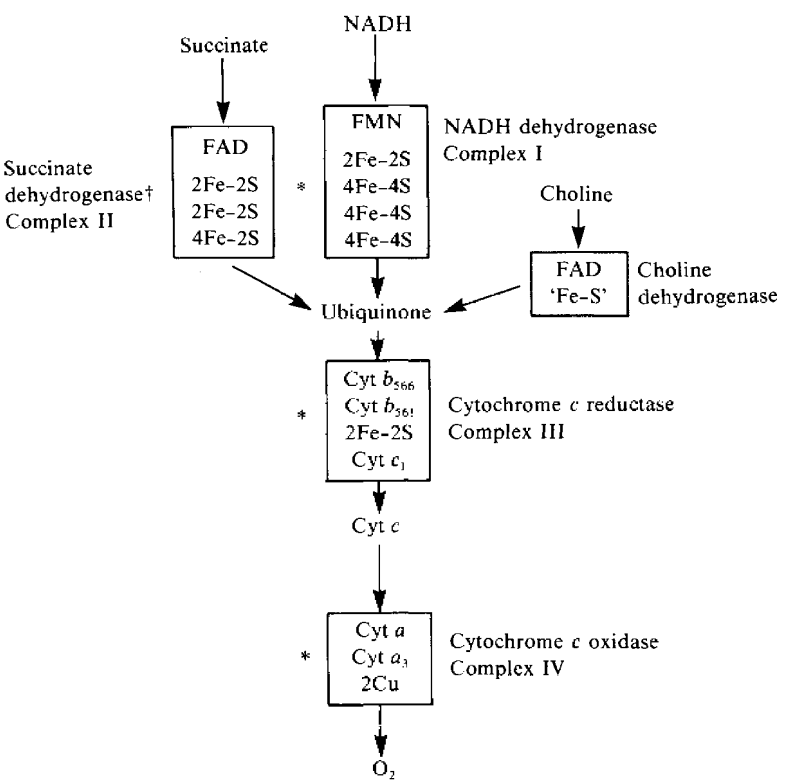


Figure 69 The respiratory chain in mitochondria

62.1.13.4.3 *Respiratory chains in* Escherichia coli

The respiratory systems of bacteria are of especial interest[1435] and complexity in view of their ability in some cases to use alternative substrates as terminal electron acceptors, depending upon the environmental conditions. This will be illustrated with reference to *E. coli*, which has been reviewed recently.[1436] The advantage of studying respiration in this organism is that, by choice of growth conditions, the pathways of electron transport can be manipulated. In addition, mutants are available which are defective in certain respiratory components.

E. coli is a facultative anaerobe, and so while it can grow anaerobically in the gut, it can also use dioxygen as the terminal electron acceptor. The three principal respiratory chains of *E. coli* are linked to fumarate, nitrate and dioxygen.

E. coli uses nitrate as a terminal electron acceptor through a respiratory, dissimilatory nitrate reductase whose synthesis is induced when nitrate is provided, and which is repressed by oxygen. Nitrate reductase is discussed with other molybdoenzymes in Section 62.1.9, and catalyzes the reduction of nitrate to nitrite. The enzyme is isolated from the cytoplasmic membrane of *E. coli*, and contains three subunits (α, β and γ) although the γ-subunit may be absent in some preparations. The γ-subunit is a *b*-type cytochrome, and the α-subunit is reported to be the catalytic subunit. The enzyme contains a number of iron–sulfur clusters, including a HiPIP and at least two ferredoxins.[1054,1437]

The site of nitrate reduction is on the inner side of the cytoplasmic membrane, even though the enzyme itself spans the membrane. This requires the presence of a transport process for nitrate. An electroneutral nitrate/nitrite antiporter seems a reasonable proposal, and has been described for *Paracoccus denitrificans*.[1439]

Nitrate respiration can support the synthesis of ATP, while proton pumping has been quantified for several physiological substrates. Stoichiometries of about $4H^+/NO_3^-$ and $2H^+/NO_3^-$ have been found for L-malate and formate, and succinate, D-lactate and glycerol respectively. There is evidence that about one mole of ATP is synthesized by oxidative phosphorylation per mole of nitrate reduced.[1440]

Membranes from nitrate-grown cells contain many cytochromes and dehydrogenases, including cytochromes *b*, *d* and a_1. One of the *b*-type cytochromes is specifically associated with the nitrite reductase, and another with formate dehydrogenase whose synthesis is also induced by the presence of nitrate. These components have been reviewed.[1436]

Table 29 Subunit Structures and Other Properties of Fumarate Reductase and Succinate Dehydrogenase from *E. coli*[a]

	Fumarate reductase	*Succinate dehydrogenase*
Subunit structure		
One flavoprotein	66 052	64 300
One iron-sulfur protein	27 092	26 600
Anchor proteins	15 000, 14 000	14 200, 12 800
Prosthetic groups		
Flavin	[8α-N^3-histidyl]FAD	[8α-N^3-histidyl]FAD[b]
[2Fe-2S] (mV)	$E_m = -45$	$E_m = -20$
[2Fe-2S] (mV)	$E_m = -275$	$E_m = -220$
HiPIP (mV)	$E_m = -60$	$E_m = +100$
Kinetic parameters (μmol dm^{-3})		
K_m for fumarate	17 (470)	450
K_m for succinate	1000	260

[a] Data taken from Table 2 in ref. 1436.
[b] For ox heart enzyme, which has identical peptide sequence adjacent to the flavin.

Fumarate is able to serve as an electron acceptor in anaerobic respiration, as it may be reduced reversibly to succinate in a two-electron process. The succinate–fumarate couple may therefore be utilized as an oxidant or reductant in the respiratory chain, and so differs from the other examples given in this section. These two reactions are catalyzed by succinate dehydrogenase and fumarate reductase, which have many similarities in subunit structure. These are shown in Table 29. Although they are different enzymes, the fumarate reductase can substitute for succinate dehydrogenase under certain conditions. The synthesis of succinate dehydrogenase is induced

under aerobic conditions and repressed under anaerobic conditions, while that of fumarate reductase is repressed in the presence of dioxygen or nitrate and induced in anaerobic conditions in the presence of fumarate.

The *E. coli* fumarate reductase consists of two polypeptides, a flavoprotein and an iron-sulfur protein. Overproduction of fumarate reductase results in the accumulation in the cytoplasm of a soluble form of the enzyme after the membrane sites are saturated. Two additional hydrophobic peptides (15 000 and 14 000 molecular weight) are necessary for the soluble two-subunit form of fumarate reductase to become associated with the membrane.[1441] This suggests that the protein does not span the membrane and is located in the cytoplasmic compartment of the cell.

ESR studies on fumarate reductase *in situ* have suggested[1436] the presence of two [2Fe-2S] clusters and a HiPIP cluster. Examination of the occurrence of cysteine residues in the two peptides and a comparison with succinate dehydrogenase suggests that the two-iron centres are in the smaller iron-sulfur protein, while the [4Fe-4S] centre may be in either subunit.

Proton translocation, the generation of a protonmotive force and oxidative phosphorylation have all been demonstrated in fumarate respiration, but there is poor correlation between the experimentally determined parameters. A number of energy-dependent transport processes for solutes, such as lactose and certain amino acids which are linked to the reduction of fumarate, have been reported.[1442,1443] Cytochromes are not involved in electron transport to fumarate from glucose as a heme-deficient mutant can grow anaerobically in glycerol with fumarate. Nevertheless, these fumarate-dependent active transfer processes could not be demonstrated in the cytochrome-deficient cells. This has led to the suggestion that cytochrome *b* is necessary for coupling electron transport to proton translocation, although this conclusion is not certain.[1444]

A range of redox centres have been found in the membranes from cells grown on glycerol and fumarate including menaquinone, ubiquinone, the iron-sulfur centres of fumarate reductase, cytochromes *d*, *b* and a_1, other iron-sulfur centres and molybdenum. Some of these centres may be assignable to specific enzymes, such as molybdenum to formate dehydrogenase. Other dehydrogenases (for NADH and lactate) are also present, and are linked to the cytochromes by menaquinone. However, there have been relatively few studies on the function of these components.

Reference has been made in Section 62.1.12 to the cytochromes in *E. coli* which are believed to function in electron transfer to dioxygen as the terminal acceptor, namely cytochromes *o*, *d* and a_1. In addition, a number of other oxidants may be linked to the *E. coli* respiratory chain.

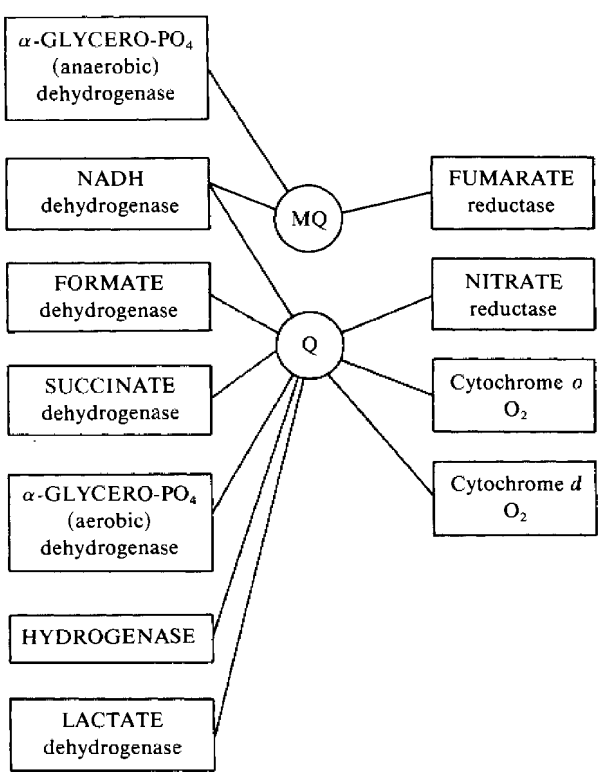


Figure 70 Schematic representation of the respiratory chains in *Escherichia coli*

These include nitrite and trimethylammonium oxide. Nitrite undergoes a six-electron reduction to give ammonia in a reaction catalyzed by a nitrite reductase. Nitrite reductase activity with lactate and formate has been reported, although other donors may support the reduction of nitrite. It should be noted that at least three pathways in *E. coli* exist for the reduction of nitrite.

This short account has emphasized the nature of the terminal redox component of each chain. These are linked *via* quinones to a range of dehydrogenases, including formate, NADH, succinate and lactate dehydrogenases, as shown schematically in Figure 70. These dehydrogenases may contain cytochromes, flavins, iron–sulfur proteins and molybdoenzymes, as noted for some cases in Figure 69. It appears accepted now that in *E. coli* it is unrealistic to postulate a linear flow of electron transport to the terminal electron acceptor, and that it is best viewed as a number of segments, many of which can coexist.

62.1.14 THE NITROGEN CYCLE

The nitrogen cycle is represented in Figure 71, which shows the various transformations that take place in nature between inorganic compounds of nitrogen, and also the incorporation of inorganic nitrogen into organic nitrogen compounds, which are then built up into major essential compounds through a range of biosynthetic pathways.

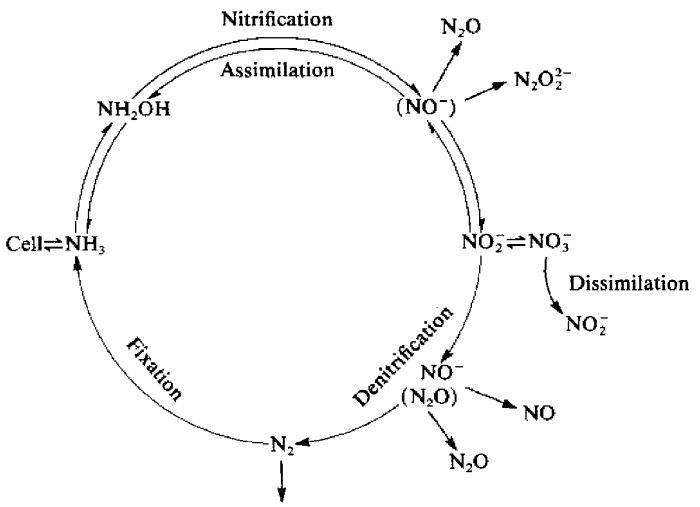


Figure 71 The nitrogen cycle

Ammonia is oxidized in nature to nitrate *via* several intermediates in the process of nitrification. Nitrate may be reduced to nitrite by either a dissimilatory or an assimilatory process. Nitrite may be assimilated into the cell *via* reduction to ammonia, or it may be reduced by microorganisms to N_2O and N_2 in denitrification. A major part of the total nitrogen in this pathway is lost to the atmosphere. However, in turn, atmospheric dinitrogen is converted to ammonia by various bacteria in nitrogen fixation.

There is a great interest in all aspects of the nitrogen cycle from a practical point of view.[1445,1446] A great deal of nitrate fertilizer (estimated to be about one third of the amount added, in the case of the United Kingdom) is leached out into rivers and hence into the sea. This is estimated to be about 150 000 tonnes of nitrate nitrogen per year. In addition, a substantial amount is lost as gaseous compounds, particularly nitrogen oxides, and thus enters the atmosphere where it may have major environmental effects in terms of acid rain and the depletion of the ozone layer. It is essential that the use of nitrate fertilizers be matched to the ability of a crop to use it, both to avoid the build-up of toxic chemicals in the environment, and to ensure that the natural process of nitrogen fixation is encouraged. These requirements have triggered a great deal of interest in the chemistry and biochemistry of nitrogen fixation, and should lead to detailed mathematical modelling of the nitrogen economy.

In recent years, most attention has been paid to nitrogen fixation, partly in order to understand the fascinating process by which a molecule traditionally regarded as being unreactive can be reduced readily to ammonia under mild conditions, and also in the hope of establishing new processes for the industrial production of cheap nitrogen fertilizers. More recently the process of denitrification has been receiving attention, while that of nitrification has been much less studied.

62.1.14.1 Nitrogen Fixation

Nitrogen-fixing microorganisms fall into two main groups, the free bacteria and those that fix dinitrogen symbiotically. Most free nitrogen-fixing bacteria do so anaerobically, which seems appropriate for a reduction process, but other organisms may be aerobic (*e.g. Azotobacter*) or facultative (*i.e.* they may grow under aerobic or anaerobic conditions). The symbiotic organisms include the bacteria *Rhizobium* found in the nodules on the roots of leguminous plants, and lichens where the blue-green algae (cyanobacteria) are involved.[1447]

The enzyme responsible for the catalysis of nitrogen fixation has been isolated from over 20 sources, and purified from many of these. Nitrogenase is made up of two proteins, one of which contains iron (the Fe protein), while the other contains both molybdenum and iron (the MoFe protein). The molybdenum is present in an iron and molybdenum-containing cofactor (FeMoco), which is thought to be an iron–molybdenum–sulfide cluster. The molybdenum is commonly regarded to be the dinitrogen-binding site. Biological and inorganic aspects of nitrogen fixation have been reviewed many times, and will be noted as appropriate.

Very recently it has been proposed that *Azotobacter vinelandii* has a second nitrogen-fixing system that may not require molybdenum. Much of the evidence comes from studies of *A. vinelandii* mutants in which the genes coding for the nitrogenase proteins were specifically deleted or inactivated, but which failed to result in loss of nitrogen-fixing ability.[1447a] The production of the second N_2-fixing system is activated by molybdenum deficiency. The alternative nitrogenase from *A. chroococcum* is a vanadoprotein, with vanadium present in stoichiometric amounts.[1565]

62.1.14.1.1 The binding and reactivity of dinitrogen in transition metal complexes

Dinitrogen forms complexes with a wide range of transition metals.[1448,1449] It behaves as a very weak σ-donor and a good π-acceptor ligand. Structural studies show that it is almost invariably bound end-on to the metal, with an effectively linear M—N—N grouping. Cases where side-on binding of nitrogen occurs are rare, for example $[(\eta^5\text{-}C_5H_5)_2Zr(N_2)\{CH(SiMe_3)_2\}]$.[1450]

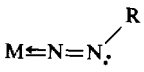
Particular attention has been paid to complexes of dinitrogen with molybdenum and tungsten, in view of the probable involvement of molybdenum as a dinitrogen-binding site in nitrogenase. In fact, the most relevant studies on model compounds have been those involving these metals. Many examples are known of complexes of the stoichiometry $[M(N_2)_2(P)_4]$, where M = Mo or W, and P = neutral phosphine. Complexes with chelating diphosphines have also been important. The protonation and acylation of dinitrogen in such complexes gave the first definitive evidence that mononuclear coordinated dinitrogen could undergo reactions in model systems appropriate for nitrogenase. It is also noteworthy that N_2 can compete with ligands such as azide and ammonia for the N_2 site in $[M(N_2)(Ph_2PCH_2CH_2PPh_2)_2]$.

At one time there was much interest in the preparation of dinuclear complexes, as it was thought that dinitrogen might bridge Mo and Fe in nitrogenase. This is now recognized to be unnecessary.

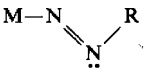
The complexes $[M(N_2)_2(\text{tertiary phosphine})_4]$ (M = Mo or W) are protonated on treatment with acid. Reaction of $[W(N_2)_2(PMe_2Ph)_4]$ with acid in methanol gives 1 mol N_2 and up to 2 mol NH_3, while the molybdenum analogue gives 1.5 mol N_2 and about 1 mol NH_3. Binding of dinitrogen to a transition metal results in polarization and greater reactivity to electrophilic attack, as there is a greater contribution from π-back bonding than from σ-donation. Protonation and reduction lead to the formation of ammonia.

The detailed pathway for these reactions has been much studied. The first protonation of N_2 bound at a mononuclear site will give the diazenido ligand ($M—N_2H$). The second protonation (and reduction) will give either the diazene (HNNH) or a hydrazido(2−) ligand (NNH_2), depending upon the site of protonation. The diazenido ligand may take up a linear, bent or side-on form, depending upon the electronic requirements of the metal. In most cases, diazenido complexes take up the singly bent configuration (**10**), although examples of the other structures probably exist, notably the doubly bent configuration (**11**). These singly bent diazenido complexes

undergo protonation at the N^{β} atom to give the hydrazido(2−) ligand.[1452] Protonation of doubly bent species gives diazene complexes.[1453] The hydrazido(2−) complexes are now well established to be intermediates in the formation of ammonia in the reactions of $[M(N_2)_2(P)_4]$.[1454]



(10)

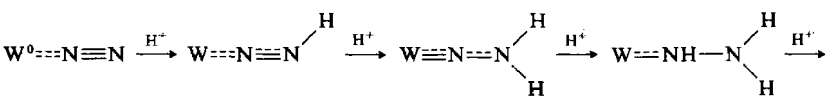


(11)

Kinetic studies on the formation of hydrazido(2−) complexes in methanol[1455] show that the mechanism involves diprotonation of a dinitrogen ligand. This removes electron density from the metal and labilizes the *cis*-dinitrogen. Methanol attacks at the vacant site and loses a proton to give *cis*-$[M(NNH_2)(OMe)(PMe_2Ph)_4]^+$. Subsequent, presumably rate-limiting, loss of a phosphine occurs with substitution by a second methanol which again is rapidly deprotonated to give $[M(NNH_2)(OMe)_2(PMe_2Ph)_3]$. A different mechanism operates in tetrahydrofuran as solvent.[1456] This mechanism accommodates the fact that under certain conditions (with *trans*-$[M(N_2)_2(diphos)_2]$ and HCl) the reaction leads to the formation of hydrido complexes.

The overall scheme is shown in equations (82) and (83) for the tungsten compound. The reaction is slightly different for the molybdenum compound and diverges at the hydrazido(2−) stage to give hydrazine and ammonia. The yields depend upon the complex, solvent and acid used. The mechanisms in both cases for reaction beyond the hydrazido(2−) stage are not known, but in the molybdenum complex the ligand may be released from the metal and undergo disproportionation. Recent evidence suggests this is not the case for $[MoBr_3(triphos)]$ where triphos = $PhP(CH_2CH_2PPh_2)$.[1457] It is necessary for the dinitrogen complex to include a labile monophosphine ligand for ammonia to be formed. Complexes such as *trans*-$[WF(NNH_2)(diphos)_2]^+$ are inert to further protic attack. It may be necessary for a phosphine to be replaced by an anion to increase the basicity of the hydrazido(2−) ligand.[1448]

$$cis\text{-}[W(N_2)_2(P)_4] \xrightarrow[H_2SO_4]{MeOH} 2NH_3 + N_2 + W^{VI} \tag{82}$$



$$W{=}NH{-}NH_3^+ \xrightarrow{2H^+} W{\equiv}NH + NH_3 \xrightarrow{2H^+} W^{VI} + NH_3 \tag{83}$$

In this scheme the electrons are all supplied by the metal, which undergoes a change in oxidation state of six. In nitrogenase, electrons would be supplied from the iron protein and there would be no need for large changes in oxidation state in the molybdenum.

Several approaches to models for nitrogen fixation in aqueous solution have also been developed which will not be considered; these are based upon molybdenum[1458] and vanadium.[1459,1460]

62.1.14.1.2 Nitrogenase

Nitrogenase[1461–1469] catalyzes the conversion of dinitrogen to ammonia. Production of dihydrogen always takes place alongside the fixation reaction,[1461] due to reaction between metal-bound hydrides and protons. It is now recognized that there is never less than one mol of dihydrogen produced per mol of dinitrogen fixed, and so the reaction stoichiometry is as shown in equation (84). The simplest explanation is that the binding of N_2 to the molybdenum releases one mol of H_2. This may imply that the dinitrogen is bound side-on, and so displaces two hydrides as H_2.[1462]

$$N_2 + 8H^+ + 8e^- \rightarrow 2NH_3 + H_2 \tag{84}$$

As noted earlier, nitrogenase is made up of two proteins, the iron protein, and the molybdenum-iron protein, and will be linked to an electron-transport chain. The iron protein accepts electrons from this chain (a ferredoxin or flavodoxin *in vivo*, or dithionite *in vitro*) and transfers them to the molybdenum-iron protein. The MoFe protein is then able to reduce a number of substrates in addition to dinitrogen. No replacement electron donor will function instead of the iron protein.

The Fe and MoFe proteins are easily separated from each other, and proteins from various sources will cross-combine to give an active enzyme. Both proteins are very sensitive to dioxygen.

The symbiotic nitrogen-fixing system in root nodules contains the dioxygen-binding hemoprotein, leghemoglobin, but its function is still uncertain.

The genetics of nitrogen fixation are under intensive study. This was carried out originally on *Klebsiella pneumoniae*. The original objective was the expression of the genes for nitrogen fixation (the *nif* genes) into plants, so that plants could fix nitrogen as required. The *nif* genes are complex: 17 genes are recognized at present. Three code for the production of the α- and β-subunits of the MoFe protein (*nif* D and *nif* K) and the Fe protein (*nif* H). The other genes are necessary for specification of the formation and insertion of FeMoco and for enzymes involved in the electron-transfer chain and the incorporation of ammonia by the cell. Thus, *nif* F codes for the flavoprotein flavodoxin and *nif* J for pyruvate–flavodoxin oxidoreductase. Glutamine synthetase, the enzyme that assimilates the newly fixed NH_3, is also involved. The expression of the *nif* genes is strongly repressed by ammonium ions, amino acids and dioxygen.

Advances are also being made in the more complex area of the molecular biology of symbiotic nitrogen fixation.[1469] Genes in *Rhizobia* involved in recognition, infection and nodulation have been identified, while some progress has been made with the plant genes and proteins involved in the development of root nodules.

62.1.14.1.3 The iron protein

This is made up of two identical subunits with a molecular weight in the range 55 000–73 000, depending upon its origin. The Fe protein has two binding sites for MgATP, and is generally accepted to contain four Fe and four S^{2-}, which can be extruded as a single [4Fe–4S] cluster. The role of the [4Fe–4S] cluster is assumed to be that of electron transfer to the MoFe protein. However, the number of unpaired electrons was reported to be less than one, while the centre appeared to behave as a two-electron donor/acceptor. This suggested that a second paramagnetic centre was present.[1470] These results have since been viewed in terms of another non-ESR-active iron centre, which is a damaged form of the [4Fe–4S] cluster.[1468] Independent studies suggest that the oxidized iron protein from *Azotobacter vinelandii* nitrogenase can contain a 2Fe protein formed by degradation of the 4Fe protein.[1471] This is an important observation that may have wider significance.

The reduced form of the Fe protein from *A. vinelandii* nitrogenase provides cysteine-97 and -132 as ligands for the Fe–S centre, which is bound symmetrically between subunits.[1472] The protein undergoes a conformational change on binding MgATP, which results in a decrease in E_0 of *ca.* 100 mV, while the ESR spectrum becomes more axial and there are changes in the MCD spectrum. The MgATP is only hydrolyzed by the Fe protein when complexed with the MoFe protein.

The clusters in nitrogenase are shown in Figure 72.

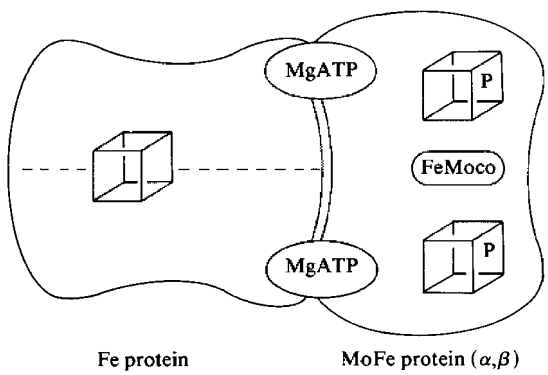


Figure 72 Schematic representation of nitrogenase

62.1.14.1.4 The molybdenum–iron protein. The P clusters

This protein contains two types of subunit of molecular weights 50 000 and 60 000, with an overall arrangement $\alpha_2\beta_2$. The total molecular weight is thus in the range 220 000–245 000, depending upon the source (*A. vinelandii*,[1473] *Klebsiella pneumoniae*[1474] and *Clostridium*

pasteurianum[1475]). The MoFe protein contains 2 mol Mo, about 30 mol Fe and about 30 mol S^{2-}, although there is considerable variation in the analytical results. The presence of clusters in the protein has been investigated by a range of spectroscopic techniques. Mössbauer measurements indicate the presence of four [4Fe-4S] clusters, and 12 iron atoms in two clusters each containing six iron atoms. These two larger clusters appear to be identical to the iron-molybdenum cofactor (FeMoco) which can be extracted from the iron-molybdenum protein using *N*-methylformamide.[1476] The cofactor does not contain protein and has an $Mo:Fe:S^{2-}$ stoichiometry of 1:6:8-9 in the case of *Cl. pasteurianum* nitrogenase.[1477] The use of core-extrusion techniques has confirmed that four [4Fe-4S] clusters are present in the MoFe protein in addition to the FeMoco.[1478-1479]

These [4Fe-4S] clusters (P clusters) from the MoFe protein differ from normal [4Fe-4S] clusters, as demonstrated by MCD and Mössbauer measurements.[1480,1481] The P clusters contain three iron atoms (D atoms) which differ from the fourth. In the MoFe protein from *A. vinelandii* the minor component of the P cluster appears to be a high-spin Fe^{II} in a tetrahedral sulfur environment. The D centres also appear to be Fe^{II} in the resting enzyme, giving an unusually reduced level for the cluster. As all four iron atoms are Fe^{II}, the Mössbauer evidence for two types of iron atom in ratio 3:1 may be interpreted in terms of variation in the non-sulfide ligands, although other explanations are possible.

62.1.14.1.5 The iron–molybdenum cofactor

This has been isolated from a range of nitrogen-fixing organisms, and appears to be identical in all cases except when an inactive form is produced by mutants deficient in certain of the *nif* genes. It differs from the molybdenum cofactor found in a number of molybdoenzymes (Section 62.1.9).

The environment around the metal atoms in the cofactor is mainly sulfide, but ligands such as citrate, phosphate, chloride, water, hydroxide or dithionite have been suggested to be present. The essential role of the cofactor is shown by the fact that addition of the cofactor to a cofactor-deficient protein from a mutant organism restores nitrogen-fixing activity. The nitrogenase from *nif* V mutants of *K. pneumoniae* contains an altered form of the iron–molybdenum cofactor. The enzyme reduces dinitrogen at a lower rate than normal, and evolves dihydrogen in a reaction which is inhibited by CO, a unique distinction from the enzyme from the wild-type organism. When incorporated into an FeMoco-deficient protein, the resulting MoFe protein, in combination with the Fe protein, exhibited poor N_2 fixation activity and its H_2 evolution activity was inhibited by CO. This provides good evidence that the FeMoco is the site at which dinitrogen is reduced. It appears likely that the FeMoco is incompletely formed, possibly differing in the nature of the non-sulfide ligands from the active FeMoco.[1482] The ESR spectra of the two forms of FeMoco do not differ very much. Since the unpaired electron associated with the ESR spectrum of FeMoco is largely located on the iron atoms,[1483] it seems that the differences between the two forms may involve some modification of the molybdenum environment, and so affect substrate binding. This provides the first substantial evidence to support the view that molybdenum is the site for dinitrogen.

Inactive MoFe protein may also be isolated from the nitrogenase of *nif* B mutants of *K. pneumoniae*.[1484] Addition of FeMoco results in activation up to 40% of normal activity, apparently because only one mol of FeMoco could be added. The *nif* B^- preparation appeared to contain one atom of non-FeMoco Mo, and so formed the MoFe protein with two Mo but only one FeMoco. This suggests that the two FeMoco sites in wild-type MoFe protein operate independently.[1485] The schematic representation of nitrogenase shown in Figure 72 thus contains two peptides, two P clusters and one FeMoco group.

62.1.14.1.6 Structure of the iron–molybdenum cofactor

A number of molybdenum–iron–sulfide clusters have been synthesized as models for the cofactor.[1478,1479,1486] At present there is no synthetic model which reproduces all of the spectroscopic properties of the cofactor. The ultimate test of a synthetic cluster would be its incorporation into the MoFe protein. Some clusters are shown in Figure 73.

EXAFS spectroscopy has been used to probe the molybdenum sites in the MoFe protein and the cofactor, and the iron sites in the cofactor. The Mo EXAFS data suggest the presence of four S atoms at 2.35 Å, two to three Fe atoms at 2.72 Å and one to two additional S atoms at about

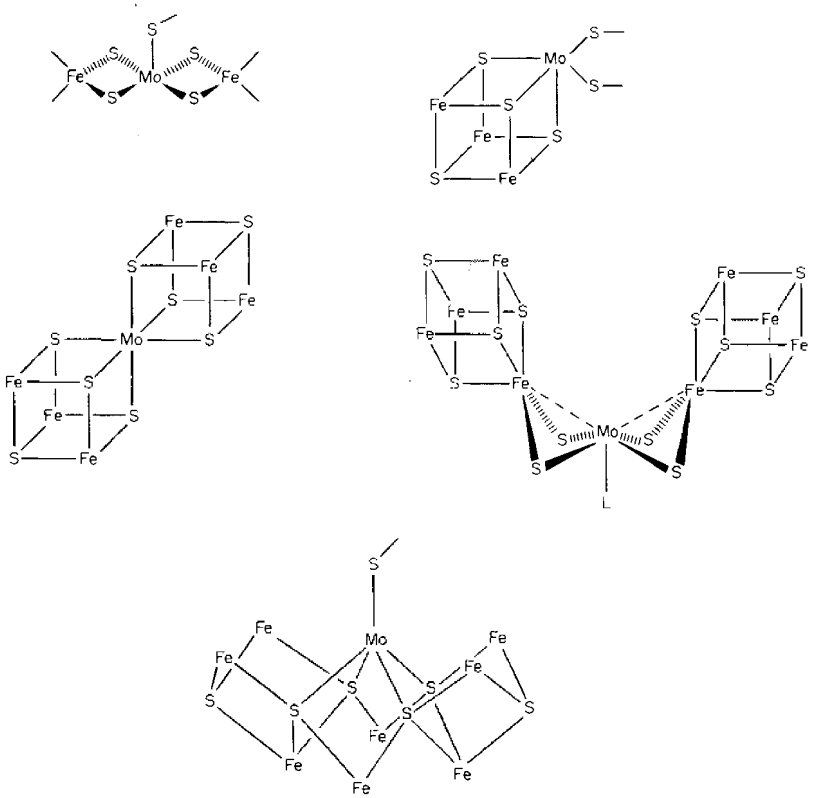


Figure 73 Some Mo–Fe–S clusters. The coordination sphere of the iron atoms is completed by thiolate ligands

2.47 Å from Mo, while there is no evidence for the presence of Mo=O, Mo=S or Mo—Mo interactions.[1487-1489] EXAFS studies have been performed on several classes of model compounds, including double-cubane clusters with $MoFe_3S_4$ cores,[1490] those with MoS_4 units $[(PhS)_2FeS_2MoS_2]^{2-}$ or $[S_2MoS_2FeS_2MoS_2]^{3-}$,[1491,1492,1493] and single-cubane structures.[1490] Some of these structures are shown in Figure 73. They all contain one Mo per cluster in accord with the stoichiometry of FeMoco. Iron EXAFS data on the cofactor suggest that the iron atoms in FeMoco have an average of 3.4 ± 1.6 S(Cl) atoms at 2.25 Å, 2.3 ± 0.9 Fe atoms at 2.66 Å, 0.4 ± 0.1 Mo atoms at 2.76 Å and 1.2 ± 1.0 (N) atoms at 1.81 Å as nearest neighbours.[1494] The large standard deviation in the number of S and Fe atoms may be due to the presence of different iron sites with varying sulfur and iron neighbours.

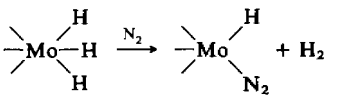
The iron EXAFS data are suggested to be consistent with but not restricted to a structure for the cofactor of either two Fe_3S_3 units bridged by a molybdenum atom, or as in the $MoFe_7S_6$ core found for the cluster $[L_3MoFe_7S_6(SR)_7]^{2-}$, which invólves a cube of metal ions with quadruply bridging sulfurs occupying the six faces of the cube.[1495] However, this stoichiometry is inconsistent with recent analytical data, and with ^{57}Fe ENDOR measurements[1496] on the MoFe protein, which show six peaks indicative of six non-equivalent iron sites within the cluster. ^{95}Mo ENDOR data have been interpreted in terms of a molybdenum atom structurally integrated into a cluster of six iron atoms.[1497] Thus, the cofactor has a remarkably complicated structure.

62.1.14.1.7 The reactivity and mechanism of nitrogenase

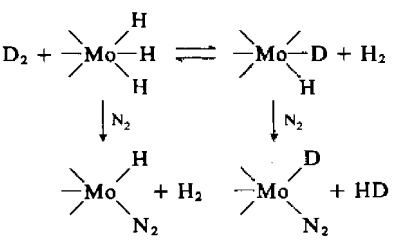
Nitrogenase catalyzes the reduction of a number of substrates in addition to N_2 and H^+. Acetylene is reduced to ethylene, and nitrous oxide to dinitrogen, while azide undergoes reduction to N_2 and NH_3. In the last two cases the product N_2 is not reduced further, implying that it is not in the correct binding position for reduction. The presence of multiple sites on the MoFe protein suggested by this observation is also supported by the non-competitive nature of the inhibition shown by some of these compounds. The reduction of acetylene has been used as a marker reaction for nitrogenase activity.

Hydrazine may be obtained from nitrogenase that is reducing dinitrogen when the enzyme is rapidly quenched with acid or alkali.[1498] It does not accumulate in solution during the reduction under physiological conditions, and arises from reactions of protons or solvents, in an acid/base-catalyzed reaction, with a dinitrogen hydride which is an intermediate in the reduction of dinitrogen. The very low concentrations of hydrazine are detected by the use of *p*-dimethylaminobenzaldehyde. The hydrazido(2−) complexes of tungsten with phosphine ligands are the only examples of complexes of possible intermediates which give hydrazine in equal yield after treatment with either acid or alkali.[1499] Furthermore, the hydrazido(2−) intermediate seems to have greater stability than other metal-bound partially reduced dinitrogen species.[1449] These lines of argument suggest that hydrazido(2−) is an intermediate in nitrogen fixation.

The evolution of dihydrogen on binding of dinitrogen has been attributed to the displacement of hydrides from a trihydridomolybdenum site (equation 85). If nitrogenase functions under an atmosphere of 50:50 D_2:H_2, then HD is produced. This is also consistent with a scheme involving molybdenum-bound hydrides (equation 86).



(85)



(86)

It is now accepted that the reduced iron protein binds two moles MgATP, followed by a change of conformation and a decrease in redox potential. The $(MgATP)_2(Fe)^-$ adduct complexes the MoFe protein (one of the two independently functioning halves of the tetrameric $\alpha_2\beta_2$ structure). This is followed by hydrolysis of two moles MgATP and the transfer of one electron to the MoFe protein (and ultimately to the bound substrate). The oxidized Fe protein is reduced under physiological conditions by transfer of electrons from pyruvate, *via* pyruvate:flavodoxin oxidoreductase and flavodoxin.[1500] *In vitro* sodium dithionite is usually used and involves $SO_2^{\cdot-}$ as the active species.[1501] The inhibition of this reaction by the MoFe protein has allowed the rate of dissociation of the $(Fe)(MgADP)_2$ protein from the MoFe protein to be measured. Comparison with the steady state rate of substrate reduction shows that this dissociation reaction is the rate-limiting step in the catalytic cycle for substrate reduction.[1501] This is substrate independent and accounts for the observation that the total electron flux through nitrogenase is independent of substrate.

Detailed studies are available on the mechanism of nitrogenase from *Klebsiella pneumoniae*, which are based upon kinetic data for the evolution of H_2 and the reduction of N_2.[1502-1505] These data have been simulated using independently determined rate constants for the oxidation and reduction of both Fe and MoFe proteins, and by assigning to various intermediate forms of the MoFe protein the ability to evolve H_2 and bind and reduce N_2. Eight consecutive electron-transfer cycles are required for best simulation. Furthermore, these studies allow the unusual damped oscillation shown by the concentration of the enzyme-bound intermediate that yields N_2H_4 on quenching in acid or alkali to be simulated. They also provide an explanation for the very long turnover time (about 1.5 s) for the reduction of dinitrogen to ammonia required by nitrogenase and for the high concentration of the enzyme *in vivo*. This group of papers presents a unified view of nitrogenase action that accommodates the available kinetic data. It is proposed that the Fe protein can bind at two independent sites on the MoFe protein, and that in addition to supplying electrons for reduction of dinitrogen, it has the role of preventing evolution of dihydrogen from reduced MoFe protein. The Fe protein thus causes the MoFe protein to function as nitrogenase and not as hydrogenase. Protons are required at the active site to protonate N_2 and its intermediates to give ammonia. However, protons will also react with molybdenum-bound hydrides to give dihydrogen. Protons must be able to gain access to the active site as dihydrogen is evolved in the absence of substrate, but this access must be controlled to allow reduction of dinitrogen to compete with evolution of dihydrogen. There is a time lag in the production of

dihydrogen from nitrogenase after initiation of reaction under argon, and where the proton is the only reducible substrate. The H_2 evolution simulations show that this time lag can be linked to the rate of dissociation of the oxidized iron protein from the reduced MoFe protein. The MoFe species that has received two electrons from the Fe protein but has only undergone one slow protein dissociation step cannot evolve H_2 on quenching with acid. Only after the second slow protein dissociation step does this happen, *i.e.* when the oxidized Fe protein is off the MoFe protein. The simplest explanation is that the presence of the oxidized Fe protein bound to the reduced MoFe protein prevents access to H^+. Dihydrogen can only be evolved after two rate-limiting dissociations of the oxidized protein. Thus, control of evolution of dihydrogen is obtained by kinetic means, which accounts for the slow turnover time of nitrogenase, and hence its high concentration *in vivo*.[1502]

The fact that the oxidized Fe protein has to be dissociated from the MoFe protein before it can be reoxidized suggests that there is only one electron-transfer site on the Fe protein. The tetrameric MoFe protein contains four MgATP-binding sites, so that each dimer will have two each, which may complement the two MgATP-binding sites on the Fe protein. In this case, the two MgATP molecules may serve to bridge the Fe protein and the MoFe protein, providing a protected region where substrate reduction and electron transfer occur (Figure 72). This would result in the exclusion of protons from these sites and hence prevent evolution of dihydrogen.

The detailed sequence of chemical events occurring at the substrate reduction site during the catalytic cycle is still unclear. Electron transfer in nitrogenase is a complex process in view of the number of redox centres available to receive and transfer electrons. The relative redox potentials of these centres will determine the distribution of electrons at equilibrium. Intramolecular electron transfer in the MoFe protein of nitrogenase from *Klebsiella pneumoniae* has been studied by ESR techniques. Oxidation of the dithionite-reduced MoFe protein by ferricyanide results in the removal of electrons from the P clusters until the $[4Fe\text{-}4S]^+$ oxidation level is reached for both clusters. Subsequently, electrons are removed either from FeMoco (to give $FeMoco^+$) or from the P cluster to give $[4Fe\text{-}4S]^{2+}$. In addition, intramolecular transfer may take place from FeMoco to $[4Fe\text{-}4S]^{2+}$ clusters.[1506] The rate of intramolecular decay of the ESR signals attributed to the P $[4Fe\text{-}4S]^{2+}$ centres is the same as the rate of enzyme turnover, suggesting that both processes may be linked to the dissociation of the oxidized Fe protein.

In summary, a number of features of the nitrogenase-catalyzed reduction of dinitrogen may be noted.

(1) The reaction involves eight electron-transfer reactions to the MoFe protein. The way in which electrons are then transferred to the substrate is uncertain.

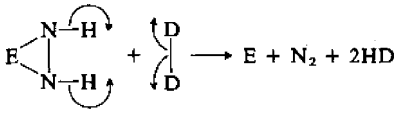
(2) Each of these electron-transfer reactions is followed by rate-limiting dissociation of the iron protein, allowing access of H^+ to the active site.

(3) In the absence of N_2, electrons are transferred to the MoFe protein, with the formation of molybdenum-bound hydrido groups by reduction of protons.

(4) Binding of N_2 results in displacement of H_2 from a trihydrido (equation 86) or a dihydrido species.[1503] This results in a transfer of two electrons to N_2.

(5) The reduction of N_2 probably involves the intermediate formation of $(Mo{=}N{-}NH_2)$, while N—N bond cleavage to give the first molecule of ammonia probably yields enzyme-bound metallo-nitrido $(Mo{\equiv}N)$ or -imido $(Mo{=}NH)$ intermediates, which are then converted to the second molecule of ammonia.[1503]

Other mechanisms have been postulated for nitrogenase. The principal alternative scheme[1507] involves a bound diazene intermediate, which is then suggested to be reduced further to a hydrazine species in the fixation reaction, but which in the presence of dihydrogen undergoes the decomposition shown in equation (87). This accommodates the formation of HD during turnover of the enzyme under H_2/D_2. The overall reaction for HD production is shown in equation (88), which is catalyzed by dinitrogen. In the scheme described earlier, the inhibitory action of dihydrogen is ascribed to the displacement of dinitrogen from the active site.



$$\longrightarrow E + N_2 + 2HD \qquad (87)$$

$$2H^+ + 2e^- + D_2 \rightarrow 2HD \qquad (88)$$

62.1.14.1.8 The sensitivity of nitrogenase to dioxygen

The destructive effect of dioxygen on the iron and molybdenum-iron proteins is thought to result from the oxidation of the clusters, and the formation of superoxide and peroxide which oxidize the proteins irreversibly. In view of this, it is remarkable that aerobic and facultative organisms can fix dinitrogen. The cyanobacteria evolve dioxygen photosynthetically and simultaneously fix dinitrogen![1447]

A number of strategies have been adopted by microorganisms to protect nitrogenase. The strict anaerobes such as *Clostridium pasteurianum* clearly avoid dioxygen. The cyanobacteria protect against dioxygen by locating their nitrogenase in specialized cells, heterocysts, which have a thick cell wall. The aerobic *Azotobacter* removes dioxygen through its high respiration rate. *Azotobacter* ceases fixing dinitrogen on exposure to high concentrations of O_2, possibly through a conformational change in nitrogenase to give an inactive but O_2-insensitive form. Certain cyanobacteria stop the synthesis of nitrogenase on exposure to high concentrations of O_2, but resume this on removal of the excess dioxygen.[1508,1509] The unicellular cyanobacterium *Gloeocapsa* sp. loses its ability to reduce acetylene when incubated with EDTA. It is suggested that EDTA depletes the cyanobacterial cells of Ca^{2+}, and thereby destroys a Ca^{2+}-dependent process by which nitrogenase is protected from inactivation by dioxygen.[1510]

62.1.14.2 The Reduction of Nitrate

As noted in Section 62.1.9.6, reduction of nitrate may occur by assimilatory or dissimilatory pathways. In the former case, the nitrate produced is reduced further to ammonia, which is incorporated into the cell. In the latter case, nitrate is reduced anaerobically to nitrite, serving as an electron acceptor in the respiration of facultative or a few obligate anaerobic bacteria. The example of *Escherichia coli* has been considered in Section 62.1.13.4.3. This process is usually terminated at nitrite, which accumulates around the cells, but may proceed further[1511] as nitrite-linked respiration in the process of denitrification.

Both assimilatory and dissimilatory nitrate reductases are molybdoenzymes, which bind nitrate at the molybdenum. EXAFS studies[1050] have shown that there are structural differences between the assimilatory nitrate reductase from *Chlorella vulgaris* and the dissimilatory enzyme from *E. coli*. The *Chlorella* enzyme strongly resembles sulfite oxidase[1050,1053] and shuttles between mon- and di-oxo forms, suggesting an oxo-transfer mechanism for reduction of nitrate. This does not appear to be the case for the *E. coli* enzyme, for which an oxo-transfer mechanism seems to be unlikely. The *E. coli* enzyme probably involves an electron transfer and protonation mechanism for the reduction of nitrate.[1056] It is noteworthy that the EXAFS study on the *E. coli* nitrate reductase showed a long-distance interaction with what could be an electron-transfer subunit.

While reduction beyond nitrite requires the synthesis of nitrite reductases, there is one case (from *E. coli*) where the nitrate reductase is suggested to reduce nitrite to dinitrogen monoxide.[1512]

62.1.14.3 The Reduction of Nitrite

While this formally may follow assimilatory (to NH_3) or dissimilatory (to N_2) pathways, it is becoming clear that a number of non-denitrifiers are also able to produce dinitrogen monoxide by reduction of nitrite.[1513,1514] Furthermore, reduction of nitrite to ammonia by one pathway (the NADPH-sulfite reductase) does not appear to be an assimilatory process, but rather one in which catabolic reducing equivalents are removed.

62.1.14.3.1 Assimilatory nitrite reductases — reduction to ammonia

Green plants, algae, fungi, cyanobacteria and bacteria that assimilate nitrate also produce assimilatory nitrite reductases, which catalyze the six-electron reduction of nitrite to ammonia (equation 89). The formation of heme-nitrosyl intermediates has been detected in several cases,[1515] while hydroxylamine is commonly thought to be an intermediate. Added hydroxylamine is rapidly reduced to ammonia. However, no intermediates are released, and ammonia is the only product

detected. These observations suggest a series of two-electron reductions, as shown in equation (90).

$$NO_2^- + 8H^+ + 6e^- \rightarrow NH_4^+ + 2H_2O \quad (89)$$

$$NO_2^- \rightarrow NO^- \rightarrow NH_2OH \rightarrow NH_3 \quad (90)$$

E. coli has a soluble NADH-nitrite reductase, which is a dimer of two identical subunits (molecular weight 88 000 each), and contains non-covalently bound FAD, at least one [2Fe-2S] centre and one siroheme per monomer. This is in accord with the reduction of substrate in two-electron steps.

The best studied nitrite reductase is the NADPH-sulfite reductase from *E. coli*, which catalyzes the six-electron reductions of both sulfite and nitrite. This is a hemoflavoprotein with an $\alpha_8\beta_4$ subunit structure. The β-subunits contain one siroheme and one [4Fe-4S] centre. Isolated β-monomers can catalyze the six-electron reduction of substrate. ESR and Mössbauer measurements show that the siroheme and [4Fe-4S] cluster are strongly spin coupled. It appears that the siroheme and the iron-sulfur cluster behave as a single functional unit, probably having a common bridging ligand.[1517] The centres remain coupled in the one- and two-electron reduced states and also in an intermediate nitrosyl-heme complex.[1518] Reduction of nitrite with fully reduced sulfite reductase results in a number of changes in the ESR spectrum. Following electron transfer from the [4Fe-4S] cluster to the heme-substrate complex, signals typical of a nitrosyliron(II) heme were observed. This species arises within the turnover space time of the enzyme, and is present in large proportions during catalysis of the reduction of nitrite to ammonia in the presence of excess substrate and reductant.[1519]

The nitrite reductases from *Neurospora crassa*[1520] and spinach[1521] also contain siroheme and iron-sulfur clusters. Mössbauer spectra suggest that the siroheme and [4Fe-4S] centres in spinach nitrite reductase are also spin coupled.[1522]

62.1.14.3.2 The chemical pathway in denitrification

Denitrifiers have distinctive enzymes that reduce nitrogen oxy compounds, usually to N_2, and couple this reaction to phosphorylation. Denitrifiers usually convert most of the nitrogen compound to gaseous products. It is customary to postulate NO and N_2O as intermediates prior to N_2.[1523,1524] There is no doubt that nitrogen monoxide is released from denitrifying bacteria under certain conditions, and that nitrosyl-heme complexes may be identified as intermediates. However, it may be more correct to posutlate the species NO^- as the intermediate, as the nitrosyl group in the complex will be present in this form. This allows the sequence shown in equation (91) to be put forward. The pathway of conversion of nitrite to dinitrogen monoxide, a four-electron step overall, is of interest as it involves the formation of an N—N bond. There are chemical parallels in which coordinated NO^- groups dimerize to give hyponitrite ($N_2O_2^{2-}$), which decomposes to give dinitrogen monoxide, but there appears to be good evidence against hyponitrite being an intermediate in denitrification.[1525] The formation of hyponitrite by this pathway also seems to require substantial conformational changes in the nitrite reductase to bring the two heme-bound nitrosyl groups close together.[1526]

$$NO_2^- \rightarrow NO^- (NO) \rightarrow N_2O \rightarrow N_2 \quad (91)$$

$$NO^- + NO_2^- \rightleftharpoons N_2O_3^{2-} \xrightarrow[4H^+]{2e^-} N_2O + 2H_2O \quad (92)$$

Another precursor to dinitrogen monoxide could be the trioxodinitrate anion, $N_2O_3^{2-}$. The intermediacy of this species has been suggested[1526] to result from reaction of free nitrite with coordinated NO^+ to give N_2O_3, which could then undergo a two-electron reduction to give trioxodinitrate. An alternative involves the reaction of free nitrite with NO^- to give trioxodinitrate directly.[1527,1528] Coordinated trioxodinitrate would then have to undergo a two-electron reduction to give dinitrogen monoxide (equation 92). Recent isotopic work[1529] and kinetic studies[1530] show that added trioxodinitrate is not reduced with the N—N bond intact, and that reaction proceeds *via* the formation of a nitrosyl complex, possibly through reaction of the decomposition products of trioxodinitrate. Again, then, there is further support for the intermediacy of NO^- but uncertainty over the mechanism of formation of dinitrogen monoxide.

The dissimilatory nitrite reductase (cytochrome cd_1, see below) catalyzes the nitrosation of several nucleophiles by nitrite.[1531] This may occur through a heme-nitrosyl in which an NO^+ group is present. Coordinated nitrite in simple metal complexes such as $[Ru^{II}(NH_3)_5(NO_2)]^+$

exists in equilibrium (at high pH) with the nitrosyl (NO^+) species. This suggests that nitrite may coordinate to the heme centre in the nitrite reductase to give a nitro complex, which is in equilibrium with a nitrosyl (NO^+) species. This could then undergo a two-electron reduction to give an NO^- nitrosyl group.

62.1.14.3.3 The biochemistry of denitrification

Many denitrifying nitrite reductases appear to be cd_1 cytochromes (Section 62.1.5.2.4). These have been characterized from at least four bacteria: *Pseudomonas aeruginosa*, *Paracoccus denitrificans*, *Alcaligenes faecalis* and *Thiobacillus denitrificans*. In general, these enzymes are composed of two identical subunits, each of which contains one heme *c* covalently bound to the protein and a heme d_1 that is non-covalently associated. The d_1 heme is a tetracarboxylic acid, with two methyl groups and two hydroxymethyl groups as substituents on the saturated pyrrole group, and two methyl groups, a propionic acid, an acrylic acid and two formic acid groups on the unsaturated pyrroles. The name 'acrylochlorin' has been suggested.[1532]

A denitrifying nitrite reductase from *Achromobacter cycloclastes*[1533] and *Ps. denitrificans*[1534] is a copper protein, containing two moles copper per mole of protein (molecular weight 69 000). This reduces nitrite to nitrogen monoxide.

The reduction of nitrite by *Klebsiella pneumoniae* gives 5% N_2O and 95% NH_4^+. Mutants defective in the reduction of nitrite to ammonium ions produced dinitrogen monoxide at rates comparable to the parent strain. This suggests that the nitrite reductase giving N_2O was distinct from that producing NH_4^+.[1535]

Copper-deficient cells of *Ps. perfectomarinus* give N_2O rather than dinitrogen from nitrite. This has led to the interesting suggestion that the dinitrogen monoxide reductase is a copper protein,[1536,1537] but it appears that the properties of the copper protein differ from those of the dinitrogen monoxide reductase.[1538] The copper protein may well lie on the electron-transfer pathway to the N_2O reductase.

62.1.14.4 Nitrification

The oxidation of ammonia to nitrite, in the process of nitrification, is brought about mainly by autotrophic bacteria such as *Nitrosomonas* species. The oxidation of nitrite to nitrate is due to the action of *Nitrobacter* species.

62.1.14.4.1 Oxidation of ammonia by Nitrosomonas europaea

It is now well established that hydroxylamine is an intermediate, the oxygen atom being derived from dioxygen (equation 93).[1539] The formation of hydroxylamine and its subsequent oxidation to nitrite are affected differently by various inhibitors, while certain inhibitors cause an accumulation of hydroxylamine. This suggests that the two processes are independent. The presence of dioxygen is essential for hydroxylamine to be oxidized to nitrite, otherwise N_2O and NO are formed.

$$NH_3 + 2H + O_2 \rightarrow NH_2OH + H_2O \qquad (93)$$

Cell-free extracts of *N. europaea* will only oxidize hydroxylamine, probably because the enzyme responsible for the initial oxidation of ammonia is associated with the membrane and so is lost on disruption of the cell. This enzyme, ammonia monooxygenase, also catalyzes the oxidation of methane.[1540] While the methane has a higher K_m value for oxidation by ammonia monooxygenase than for oxidation by a methane monooxygenase, it is still possible that both processes would be catalyzed by ammonia monoxygenase in the natural environment.

The enzyme hydroxylamine oxidoreductase catalyzes the oxidation of hydroxylamine to nitrite. This enzyme has long been known to be rich in cytochromes, and it has now been characterized as an $(\alpha,\beta)_3$ complex of three monoheme *c*-type cytochromes (molecular weight 11 000 each) and three larger proteins each containing six *c*-type hemes and one P-460 heme.[1541,1542] The total molecular weight is about 220 000 and there are 21 *c*-type hemes and three P-460 hemes. The ESR[1543] and Mössbauer[1544] spectra of this complex enzyme are now being resolved. ESR spectroscopy in conjunction with reductive titration of the enzyme indicates that the *c*-type hemes fall

into at least four groups, having different redox potentials and protein environments. Three of these groups are characterized by g values 3.38, 1.95, 0.7; 3.06, 2.14, 1.35; and 2.98, 2.24, 1.44, but about one third of the heme iron is associated with other species. Part of this missing heme is ESR-silent, since high- and low-spin signals, which are not present in the spectrum of the resting enzyme, appear during the final half of the reductive titration. One of these additional species, of high-spin, may be due to heme P-460. This heme binds carbon monoxide and cyanide and so probably has an axial ligand that may be replaced, possibly by hydroxylamine. The range of cytochromes used by the enzyme is intriguing, and this may suggest that electrons are removed from hydroxylamine by a number of electron-transfer catalysts to the final acceptor. Complexation of hydroxylamine under anaerobic conditions results in the reduction of about 45% of the hemes.

Two soluble CO-binding cytochromes *c* have been purified[1545] from *Nitrosomonas europaea*, with apparent molecular weights of 32 000 (cytochrome c_{CO}-550, $E_m = +140$ mV) and 16 000 (cytochrome c_{CO}-552, $E_m = -50$ mV). Binding of CO to reduced cytochromes is indicative of a dioxygen-binding function. It is possible that dioxygen is transferred to intermediate species in the oxidation of hydroxylamine. Thus, an NO^- nitrosyl complex could be formed, which could undergo reaction with O_2.

62.1.15 TRANSITION METAL IONS AND ANTIBIOTICS

A number of antibiotics appear to require a transition metal ion as a cofactor.

62.1.15.1 Bleomycin

The bleomycins are a group of glycopeptides isolated from *Streptomyces verticillus* as copper complexes. They have attracted much attention because, in addition to having antimicrobial and antiviral properties, they are also important in the treatment of a number of tumours, including Hodgkin's disease. Some 200 bleomycins have now been identified, although the main component of the clinical drug is bleomycin A2.[1546,1547] Bleomycin requires a metal ion. The Fe^{II} complex is usually thought to be the active form, and to function by binding and reducing dioxygen, and then reacting with DNA with strand scission. Comparisons have been drawn with cytochrome P-450. Other metals also mediate degradation of DNA in the presence of O_2 *in vitro*, including, under certain conditions, copper,[1548] manganese,[1549] nickel and cobalt(III).[1550]

62.1.15.1.1 Structural studies on bleomycin and its transition metal complexes

The structure of bleomycin is shown in Figure 74, and contains a dithiazole group, thought to be responsible for the binding of DNA, an amino-pyrimidine–imidazole region which binds transition metal ions, and sugars.

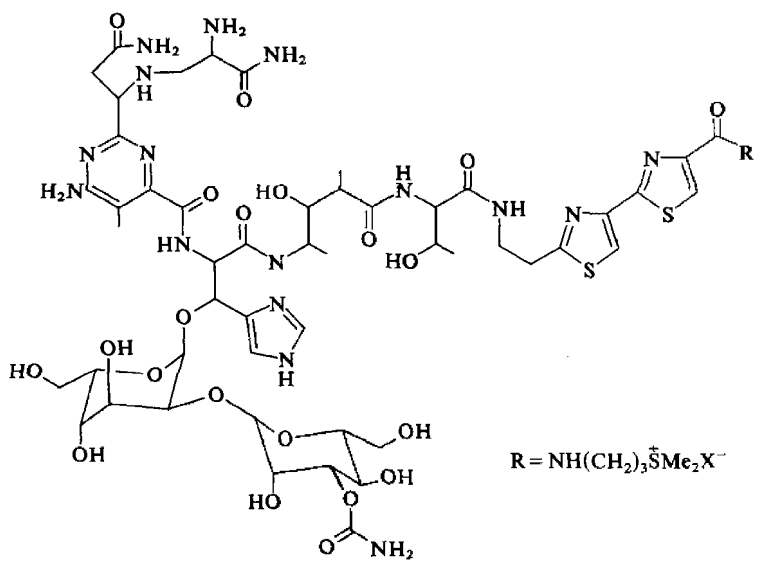


Figure 74 The structure of bleomycin

^{1}H and ^{13}C NMR measurements have suggested that Zn^{II} and Cu^{II} are bound by histidyl and pyrimidine groups, while ESR measurements show the presence of nitrogen hyperfine splitting, and suggest the presence of at least four nitrogen donors.[1551] The crystal structure of the bleomycin fragment P-3A with Cu^{II} (Figure 75) shows the copper to be bound by an axial amine group, and four in-plane nitrogens from peptide, imidazole, secondary amine and 4-aminopyrimidine.[1552] The extrapolation of this result to the structure of complexes of the intact antibiotic has been doubted, but the structure of the major product of hydrolysis of the cobalt(III)-bleomycin complex, which preserves the ligating properties of the intact drug, appears to be analogous to that of Cu^{II} bleomycin P-3A.[1553,1554]

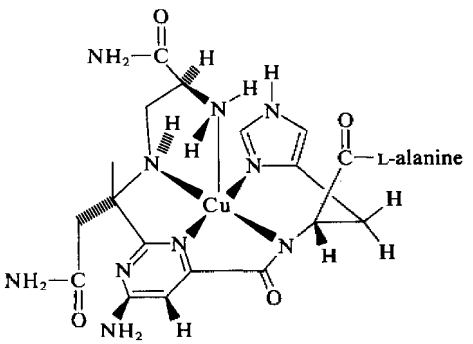


Figure 75 The Cu^{II} complex of bleomycin P-3A

62.1.15.1.2 Mechanistic aspects

The presently accepted model[1555] for the reaction of bleomycin with DNA involves the binding of an Fe^{II}-bleomycin complex to DNA, and the reduction of iron-bound dioxygen. Cleavage of DNA is known to occur by the action of the 1,10-phenanthroline complex of Cu^{I} in the presence of hydrogen peroxide, and this reaction is sustained by the presence of NADH.[1556] This provides a useful parallel for the bleomycin reaction.

Every type of DNA serves as a substrate to bleomycin, but RNA is not degraded. A role for the thiazole residues in binding DNA has been suggested, as the fluorescence intensities of these groups in the metal-free antibiotic are reduced in the presence of DNA, a view subsequently supported by NMR measurements.[1557,1558] It also appears that DNA binds to the α-amino group of the β-aminoalanine moiety in bleomycin, possibly lowering its pK_a group and promoting its coordination to the iron.[1559]

The reaction pathway appears to involve the formation of superoxoiron(III) bleomycin prior to that of 'activated bleomycin', which appears to be a peroxoiron(III) complex, although the source of the second electron is uncertain. Activated bleomycin can be synthesized directly by reaction of hydrogen peroxide with iron(III)-bleomycin. In the absence of DNA, activated bleomycin decays to the Fe^{III} complex, with damage to the antibiotic. In the presence of DNA, degradation products appear with a rate of formation equal to the rate of loss of activated bleomycin. The polymeric products of DNA degradation have not been characterized, but they decompose to give free bases, released in the sequence T > C > A > G.

62.1.15.2 Adriamycin

This anticancer drug causes the scission of single-strand DNA amongst its various biological properties. Here, too, the reaction involves binding of Fe^{II} by adriamycin and the reduction of O_2.[1560]

62.1.15.3 Bacitracin

The bacitracins are a group of polypeptide antibiotics produced by *Bacillus licheniformis*. Bacitracin A is a dodecapeptide that acts against Gram-positive bacteria, apparently by blocking the dephosphorylation of a lipid carrier intermediate C_{55}-bactoprenyl pyrophosphate, which is

essential for the synthesis of cell walls. Bacitracin is effective only in the presence of divalent metal cations, possibly to allow the formation of a complex of bacitracin A with long chain polyisoprenyl intermediates.[1561] The number of bacitracin molecules bound to cells of *Micrococcus lysodeikticus* is roughly equal to the number of bactoprenyl pyrophosphate molecules present.[1562]

The possible binding groups in bacitracin A are shown in Figure 76. ESR measurements[1563] suggest the Cu^{II} complex is square planar, with ligand groups provided by the glutamate γ-carboxyl, imidazole, the aspartate β-carboxyl and the thiazoline nitrogen, in accord with some earlier evidence[1564] for the involvement of the aspartate group.

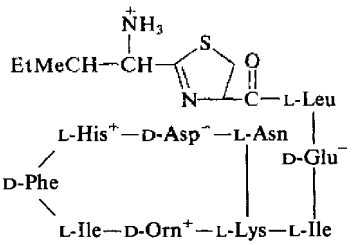


Figure 76 The structure of bacitracin A

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62.2

Uses in Therapy

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62.2.1 INTRODUCTION

Coordination chemistry can find a use in medicine in a number of ways. Coordination compounds can be used in the treatment, management or diagnosis of disease, or coordination complexes can be formed in the body to handle dysfunction due to metal poisoning. Specifically one can define four principal areas of the use of transition metal compounds in medicine. These are:
(1) The use of coordination compounds, or metal-based drugs, to treat disease. Examples are the historical use of organoarsenicals in the treatment of syphilis, the more recent use of *cis*-dichlorodiammineplatinum(II) in the treatment of certain types of cancer, and the use for 50 years of complexes of gold in the treatment of rheumatoid arthritis.
(2) The use of chelating or complexing agents to treat metabolic dysfunction. The classical example is the use of D-penicillamine to treat Wilson's disease, which is caused by an inability of the body to metabolize copper in the normal way. Another example is the use of desferrioxamine for iron overload in Cooley's anemia, which is caused by a fault in hemoglobin synthesis.
(3) The use of complexing, chelating or sequestering agents to remove heavy metal poisons from the body. We are slowly beginning to realize how serious the problem of heavy metal poisoning is, and there is likely to be increasing pressure from the public to devise methods of treating patients

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who have heavy metal poisoning. A well-known example is the excess of nickel in some industrial settings. Chelation therapy may be the only acceptable treatment.
(4) The use of coordination complexes to transport metals to specific sites in the body to aid in imaging. The classical example is the use of these complexes in radioimaging, and complexes of technetium have been used in this way to transport ^{99m}Tc to the site to be imaged. More recently, with the advent of NMR imaging of the human body, there has been interest in the use of paramagnetic complexes which go to specific sites in the body to improve the contrast in other images. Thus there is a growing area of research on the design of ligands which will go to a specific organ in the body and which can be used to take any metal as needed to that particular site.

In this chapter we shall limit our discussion to complex compounds used in the first three of these principal areas. In addition, we shall discuss briefly the role of some physiologically important elements and molecules whose coordination chemistry *in vivo* is less well defined. Throughout this chapter, the series 'Metal Ions in Biological Systems', edited by Helmut Sigel,[1] will be referred to frequently, and these references will be shown in the format, ref. 1, vol. 14, pp. 179–205, for example.

62.2.2 THERAPEUTIC USES OF COORDINATION COMPLEXES

62.2.2.1 Miscellaneous Therapeutic Compounds (Historical Perspective)

Syphilis has been recognized for four centuries and has been treated variously by mercury in the Neapolitan epidemic, by iodides in about 1835 and by bismuth. In 1909 Ehrlich introduced arsphenamine (Salvarsan) for this disease. Hg, Bi, iodides and the arsenicals (despite their very toxic side effects) remained the mainstay of drug therapy for many years. Penicillin was introduced by Alexander Fleming in 1928, but not until 15 years later, in 1943, was this new drug tried on syphilis and found to be effective against most forms, making the use of organoarsenicals largely obsolete.

There are a few common and long-known uses of heavy metal compounds which should be mentioned. The 'barium meal' is used in gastrointestinal X-rays. It is administered as barium sulfate, the high electron scattering of barium ions providing X-ray opacity. Mercurial diuretics, derivatives of propan-2-ol, work by inhibition of sulfhydryl enzyme sites. These compounds are now becoming obsolete, however.

Many inorganic compounds have been designed by chemists for specific actions. Because the biological effect depends on the structure of the complex as much as on the presence of a particular element, there is much scope for chemists in pharmacological design. Examples of some better-known preparations include the use of Mg, Al and Bi in antacids ('Bisodol' in the UK); F, Zn, Sr and Sn added to toothpastes; Al and Zr in antiperspirants; Se and Zn in antiseborrheics; Zn in healing ointments ('Zincofax' in the US); Cl and I in germicides; and Sn in tablets for boils and acne ('Stanoxyl').

In more recent times, people have become used to the idea that mood can be altered by complex organic molecules such as alcohol, opium and cocaine, but it is fascinating that a simple inorganic salt — a very small ion (Li^+) or a bit of rock (Li_2CO_3) — can alter this subtle aspect of the mind.

62.2.2.2 Anticancer Drugs

62.2.2.2.1 Platinum complexes

Probably the most well-known use of coordination complexes in the treatment of disease is that of platinum complexes in the treatment of certain types of cancer. Although a number of complexes have reached the experimental testing stage, only one compound is in general use, namely *cis*-dichlorodiammineplatinum(II), known as *cis*-platin. This drug was approved by FDA for human treatment in 1979, and by 1983 was the leading anticancer drug in the USA. This drug is used in combination therapy with either adriamycin or bleomycin and vinblastine, and it has been used most successfully in the treatment of testicular cancer, although it is used against other cancers such as ovarian or lung.

The activity of the platinum complexes was discovered accidentally by Barnett Rosenberg and coworkers when they were examining the action of electric current on the bacterium *E. coli*. The effect of the current on bacterical growth in the growth medium was to prevent cell division but to allow cell growth to continue. Establishing that the effect needed the combined action of chloride ion, oxygen, ammonia, electric current and the platinum electrodes took some time, and the paper in Nature[2] describes this fascinating detective story. Initial results suggested that the active agent

was ammonium hexachloroplatinate(IV) and it was not until sometime later that *cis*-platin was discovered to be the active agent. Rosenberg and his colleagues realized that the effects seen on the bacteria were also induced by radiation and materials such as alkylating agents, all of which were used as anticancer agents. Tests on animals revealed that *cis*-platin did have anticancer activity, and after much further testing the compound was put into general use. The historical development of these drugs is described in a number of reviews and books.[3–7] Features of the active drugs are as follows. (i) They are neutral complexes of platinum(II) or platinum(IV). (ii) They contain *cis* amine groups which are in turn *trans* to *cis* leaving groups: complexes with *trans* leaving groups are inactive. The leaving groups must be reasonably labile: compounds containing leaving groups such as cyanide, nitrite, thiocyanate or iodide, which are strongly bound to platinum(II), are inactive. (iii) The amine group must be primary or secondary: tertiary amines apparently show no activity. There is one exception to the first requirement: Rosenberg and his colleagues have reported that the platinum blues show anticancer activity, and these species are known to be cationic.

Several compounds have been identified which show better antitumor activity than *cis*-platin. Some have the advantage of higher water solubility and greater ease of administration. Sulfato-1,2-diaminocyclohexaneplatinum(II) is water soluble (0.5 mol l^{-1}), active against at least three animal tumors, and about 30 times as potent as *cis*-platin. A similar malonato complex is unique in that significant concentrations reach the brain (as tested in dog). *cis*-Diammine-1,1-cyclobutanedicarboxylateplatinum(II), carboplatin, has just been released in Britain for general use, after extensive trials.

It is thought that the platinum complexes act as anticancer agents by interacting with DNA. It was shown in early experiments that *cis*- and *trans*-platin bind most strongly to RNA, then to DNA and least strongly to proteins. When the activity was assessed as the ability to suppress the synthesis of DNA, RNA and protein, however, by measuring the uptake of tritiated thymidine, uridine and lysine, respectively, it was found that, at low doses, only the synthesis of DNA was suppressed. Another piece of evidence that the interaction was with DNA was that *cis*-platin causes lysis in lysogenic bacteria. Binding to DNA was studied by Roberts *et al.*[8] who showed that both inter- and intra-strand crosslinking took place. Roberts also argued that interstrand crosslinking was unlikely to be the important lesion on DNA. Further studies showed that binding occurred preferentially to DNA which contained high proportions of guanine and cytosine. Studies with the free bases, nucleosides and nucleotides showed that under physiological conditions (water, pH 7.6) binding occurred to guanine, cytosine and adenine, but not in any significant amount to thymine. Kinetic studies and structural studies showed that of these bases the preferred binding site was the N-7 position of guanine. This preference was confirmed by Dickerson *et al.*[9] who showed that a double-strand DNA dodecamer treated with *cis*-platin bound the platinum to the guanine N-7 positions exclusively. A persuasive argument arose that the important lesion was an intrastrand crosslink between two adjacent bases on a DNA strand. Lippard,[10] in a cleverly conceived experiment, showed that *cis*-platin was bound to a GGGG/CCCC segment of a circular DNA. He subsequently argued that similar results were obtained when *cis*-platin was interacted with the self-complementary TGGCCA sequences.[10] Complete unravelling of the sequence occurred because the binding to the two adjacent guanines caused a marked disruption of the structure. This result was consistent with many structural studies which showed that binding of DNA bases to *cis*-platin caused the bases to be at large dihedral angles to the square plane about platinum and to each other. It was expected, therefore, that the sort of binding envisaged would cause marked distortion and destruction of the DNA helix in the region of platinum binding. Reedijk *et al.*[11] showed that a single platinum atom was bound to the N-7 positions of two adjacent guanine molecules. The recent findings of Chotard *et al.*[12] and Reedijk *et al.*[11] come as something of a surprise therefore. They have shown independently that when *cis*-platin is bound to the double-strand sequences, the GG/CC hydrogen bonding is not destroyed even though the platinum atom is apparently bound to the two adjacent guanine molecules. Modeling has suggested that this can occur if the DNA strand is bent or kinked in the region of the platinum binding. The selectivity of platinum complexes in attacking tumor cells rather than normal cells, even though there is little or no preferential uptake of *cis*-platin in tumor cells, has led to the suggestion that cancer cells are deficient in some DNA repair mechanisms. DNA is constantly being damaged but various repair proteins can recognize the damaged segment and cause repair. The process of replication causes disruption of the helix at the point of replication and may involve a B → Z transformation. If this is so, it will produce a kink at the point of transformation. If this is a necessary transformation, repair proteins may ignore this site and it was suggested that the kink caused by platination in the Reedijk and Chotard models may not be repaired therefore.

Very recently, Lippard has introduced a new model which reinterprets the NMR results of Reedijk and Chotard and which is esthetically more satisfactory. Lippard and his colleagues measured the uptake of both *trans*- and *cis*-platin in CV-1 monkey cells infected with SV-40 virus particles. Initially *trans*-platin was taken up more rapidly than *cis*-platin but DNA concentrations of *trans*-platin reached a maximum after eight hours and then dropped rapidly. *cis*-Platin continued to rise throughout the whole 24 hour period of the experiments and DNA concentrations of *cis*-platin were very much higher than *trans* concentrations after 24 hours. The results were interpreted as removal of the bound *trans*-platin by the repair proteins whereas the bound *cis*-platin was not removed by the repair mechanism.

Lippard modeled the interaction of *cis*-platin with a 10 base pair DNA sequence containing a d(GpG) pair. One major difference from the results of Reedijk and Chotard was the interpretation of the NMR results. These authors interpreted the lack of exchange of the proton bound to N-1 of guanine as evidence of Watson–Crick hydrogen bonding. The Lippard model retained an N-1(guanine)···N-3(cytosine) hydrogen bond, but allowed other hydrogen bonding involving the N-4, O-2 (cytosine) and O-6, N-2 (guanine) sites. The new model has no kinks in the DNA and, viewing down the helical axis, it is difficult to differentiate the platinated and unplatinated sequences. Further, Lippard and his coworkers have determined the crystal structure of an $[(NH_3)_2Ptd(pGpG)]^{n+}$ sequence and the parameters agree very well with the model. On the other hand, a *trans*-platinated single sequence produces a d(GpXpG) or d(GpXpXpG) chelate, which will produce a loop in the DNA. Such loops have been established by Reedijk and ourselves. One notable feature of Lippard's model is a strong hydrogen bond from ammonia to a phosphate group, suggesting an explanation for the need to have at least one hydrogen atom on the amine in platinum anticancer drugs.

The minor perturbation of the DNA structure caused by *cis*-platin may well not be detected in a cell which has a deficiency in the repair mechanism, whereas a normal cell might have a more selective repair mechanism. Whether this is the mechanism of action of the platinum anticancer drugs still has to be established, but it is the first model which satisfactorily accounts for all the known chemical and structural restraints. In addition, it suggests further modeling experiments with the more effective second generation drugs.

62.2.2.2.2 Other metal complexes

(i) Copper, rhodium, palladium, ruthenium and iridium[13]

Serum copper concentrations have been shown to increase in active cancer and decrease in remission; thus it seems likely that some copper-dependent process is required for response or remission. A number of copper complexes have been tested and found to have rodent antitumor activity. There appear to be copper complexes which serve in a homeostatic fashion to prevent development of neoplasms. If this physiologic response fails at some point, tumors may be allowed to grow.

When Cu was used as a radiation sensitizer, the cytotoxic effect of radiation was proportional to the copper content of the cell. A possible mechanism is radiation-catalyzed reduction of Cu^{II} to Cu^{I} followed by oxidative destruction of nucleic acids by Cu^{I}.

Gillard and coworkers[14] pioneered the study of biological activity in Rh complexes, especially of the type *trans*-$[RhX_2L_4]Y$ where L_4 are substituted heterocyclic amine ligands. Massive filamentation, indicating an interference with cell division, is shown by many of these complexes.

A series of Pd^{II} analogs of active Pt^{II} complexes have been tested against certain tumor lines but showed no significant activity. On the whole, any activity observed has been much inferior to that of the Pt^{II} complexes, and the palladium compounds do not seem to be very promising.

Several Ru compounds have shown antibacterial activity but not antitumor activity. There is room for systematic structure studies of such complexes.

A violet solution prepared by UV irradiation of a solution of $(NH_4)_2[IrCl_6]$ in ammonia has been reported to show activity against the Ehrlich ascites tumor. The solution, which probably contains both Ir^{III} and Ir^{IV} species, also causes filamentous growth in *E. coli*.

62.2.2.3 Antiarthritis Drugs

62.2.2.3.1 Gold drugs

There has been a medicinal mystique surrounding gold since man's early history. Gold was believed to flow in the veins of Egyptian gods and goddesses, giving strength and endurance. Gold in some form has been considered a panacea from the time of Arabic and Chinese physicians in

2500 B.C. through to Paracelsus in 1500 A.D. Modern use of gold started with the report of the antibacterial activity of gold salts by Robert Koch in 1890, after which gold salts, including gold sodium thiosulfate (SANOCHRYSIN™), were used for the treatment of tuberculosis, syphilis and other disease organisms. Lande used aurothioglucose (SOLGANAL™) for various diseases, including bacterial endocarditis and rheumatic fever. A lessening of joint pain led to recommendations for trials in chronic arthritis.[15–18]

Modern chrysotherapy,[17] the treatment of rheumatoid arthritis by gold complexes, began with the work of J. Forestier in 1929. By 1935 he had reported benefit from gold salts in chronic arthritis. He first used sodium aurothiopropanolsulfonate (ALLOCHRYSINE™) and later sodium aurothiomalate (MYOCHRISIN™), SOLGANAL™ and others. Now the commonly used drugs are MYOCHRISIN™ and SOLGANAL™, both given by intramuscular injection (weekly or monthly). A newer drug, AURANOFIN™, (*S*)-2,3,4,6-tetraacetyl-1-D-thioglucose(triethylphosphine)gold(I) can be administered orally. This has the potential advantages of being given in more frequent, smaller doses, avoiding the pain of injections, and possibly resulting in fewer adverse side effects. Nevertheless, there are potential disadvantages. Serious gastrointestinal side effects have been reported in some patients and there is the problem of patient compliance with drug dosage and the difficulty of monitoring the patient for the onset of serious side effects, neither of which exists for a drug administered by an injection given in a clinic.

The modes of action of these drugs are still uncertain, but it seems likely that there are anti-inflammatory and antienzyme activities of gold(I) compounds. It may be that the drugs modulate the body's immune response in some way. Unlike iron and copper, which are essential elements, gold does not have a well-defined transport, storage or enzyme function.[17]

Gold sodium thiomalate provides a stimulus for liver, kidney and possibly other cells to change the body distribution of zinc and copper. Proteins such as metalloproteins, superoxide dismutase and metallothioneins[19] help the cell carry out this task. These essential metals are important in the physiological processes relevant to rheumatoid arthritis, and thus it also appears possible that the gold complexes may mediate their antiarthritic activity through an effect on the metabolism of zinc and copper.

Several reviews on gold therapy have appeared recently, with an emphasis on metabolism by Shaw,[19] on ligand exchange reactions by Sadler and coworkers,[20] on EXAFS and XANES studies by Elder *et al.*,[21] and on studies of gold thiolate complexes *in vivo* and *in vitro* by Brown and Smith.[22]

The chemical structures of the commonly used antiarthritis compounds gold sodium thiomalate and gold thioglucose have still not been determined, not because of lack of interest, but because of the complexity of the chemistry. Gold sodium thiomalate appears from spectroscopic evidence to contain at least one polymeric unit. Work on the structural chemistry is being pursued by several laboratories. The solution of gold sodium thiomalate sold as the drug MYOCHRISIN™ is known to be a mixture, and work on the separation and purification of its components is expected to lead to understanding of its mode of action and minimizing of its toxic side effects. There have been reports on the relationship between histocompatibility (HLA markers) and gold or D-penicillamine therapy; for example, HLA types B8 and DR3 are associated with proteinuria induced by either gold or D-penicillamine. It seems, however, that the use of HLA typing as a guide to therapy would be premature at this time.[23]

62.2.2.3.2 Copper and copper complexes

There is some evidence that localized copper imbalance is related to rheumatoid arthritis (RA) conditions. Low molecular weight copper complex concentrations in plasma and synovial fluids are increased as part of the body's natural response to RA. Secondly, when such increases are induced by copper administration, they have a powerful antiinflammatory effect. More data are required to show the medical significance of these changes. Three parameters which should be reported are (i) total copper levels (by atomic absorption spectrophotometry); (ii) total ceruloplasmin levels (by autoimmune assay); and (iii) the relative molecular weight distribution (by Sephadex gel filtration and ultrafiltration).

The wearing of copper bracelets to benefit arthritis is an apocryphal use of copper. It is not clear whether any measurable amount of copper is dissolved by the body. The average weight loss from copper bracelets is 12 mg $month^{-1}$ while they are worn. Studies show that components in human sweat could solubilize this metal and possibly aid its absorption. On the other hand, copper-coated intrauterine devices can lead to the dissolution of about 25–50 mg Cu per year. There are no studies to show whether this leads to chronic copper toxicity or whether there is a protective effect against

arthritis. A single-blind crossover study has shown copper bracelets to be effective in relieving arthritic complaints.[24] It would seem to be appropriate that the medical profession reconsider the validity of the copper bracelet.

In recent history, the therapeutic potential for copper in the treatment of rheumatic diseases was recognized by Hangartner in 1939 when he learned that copper miners in Finland were free of rheumatism. Sorenson[25] has reviewed the literature on changes in copper concentrations in patients with rheumatoid arthritis. In patients with active disease there are marked increases in serum or plasma copper, an accelerated turnover rate of ceruloplasmin, and an increase of synovial fluid copper. A number of copper-dependent enzymes are known to be required for repair of inflamed tissues.

A very large number of copper compounds have been tested for antiinflammatory activity, and various copper complexes of antiarthritic drugs have been found to be more effective than the parent drugs alone (including aspirin, D-penicillamine, ketoprofen and gold thiomalate).[25]

Forrestier, in the 1940s, believed the copper-containing compounds Cupralene (sodium 3-(allylcuprothiouredo)-1-benzoate) and Dicuprene (bis[8-hydroxyquinolinedi(diethylammonium sulfonate)]Cu(II)) to be superior to gold therapy.[24]

Dicuprene, for example, was given mixed with novocain two or three times a week (32.5 to 65 mg Cu) with a total dose of 390 to 780 mg Cu in a series. The results were good in treating RA that had been active less than one year, even if the patient had become resistant to gold therapy. Although Cupralene and Dicuprene were found to be effective and sometimes superior to gold therapy for RA and for other degenerative connective tissue diseases, nothing more was published about these drugs after 1955. They appear to have been discontinued because of sudden interest in hydrocortisone as a potential cure.

Hangartner used a preparation of copper salicylate known as Permalon (made from 12.5 mM sodium salicylate and 0.04 mM $Cu^{II}Cl_2$) to treat over 1100 patients over a 20 year period, with 89% showing benefit and few side effects. Unfortunately this therapy was discontinued when he retired in 1970.[24]

62.2.2.3.3 Superoxide dismutase

Milord, in 1974, suggested that RA may be the result of a lack of superoxide dismutase, an enzyme containing copper. Bovine Cu–Zn superoxide dismutase (SOD) has been developed as a drug (Ontosein or Orgotein) for treatment of rheumatoid and osteoarthritis. It is given by injection into knee and hip joints.[25–27] Evaluation of Orgotein efficacy against the reference drugs 'gold' and penicillamine has been carried out in Europe. Orgotein was rated comparable in effectiveness and higher in safety. It can also be used to ameliorate the side effects of high dose radiation, which is inflammatory.[26] Some copper chelates also have both SOD-like activity and antiinflammatory activity.

In summary, copper complexes, including superoxide dismutase, make up a unique group of antiarthritic drugs, being potent antiulcer agents and causing little gastrointestinal (GI) irritation. Long lasting remissions have been achieved with relatively short therapy.[24]

62.2.2.4 Treatment of Deficiencies

62.2.2.4.1 Essential trace elements

Almost all of the 90 naturally occurring elements are present in the human body. It is not surprising, considering the evolutionary process, that there is correlation between the concentration of elements in sea water and in the human body. Only about half of these elements, however, have any known biological role. The five elements which make up most of living matter — C, H, N, O and S — together with the 'macrominerals' Ca, Mg, P, Na, K and Cl are present in the body in gram per kilogram concentrations and are required daily in the diet in gram amounts. The remaining 'trace' elements are present only in milligram or microgram per kilogram concentrations. In addition, certain non-essential elements, such as Br and Rb, occur in tissues in concentrations well above those of most of the trace elements (in whole blood comparable to Zn).[28–40]

Figure 1 shows the physiological effects of (i) essential and (ii) toxic elements according to dosage. For each essential trace element there is a narrow, 'life-sustaining' concentration range. Below this range deficiency syndromes occur; above it, poisoning occurs.[3,28–30] In addition, some of the toxic elements, while having no essential function, can be administered in low concentrations in drugs and can then have beneficial effects. Many elements which were studied originally only for toxicity have turned out to be essential; indeed, for selenium, deficiency is a greater problem

than toxicity. Chromium and arsenic have essential functions. Thus additional elements which are now regarded as toxic or harmless are likely to be proved essential in the future. Some 16 elements are considered to be possibly essential and some 18 others, including Ag, Au and Hg, are under special consideration.[34] The trace elements act mainly in enzyme systems, for example zinc is present in over 160 enzymes with many functions. Only four molybdenum enzymes and one selenium enzyme are known. The enzymes regulate larger masses of substrate and the substrate in turn may have a regulatory function, so that there is amplification of the effect of the trace element.

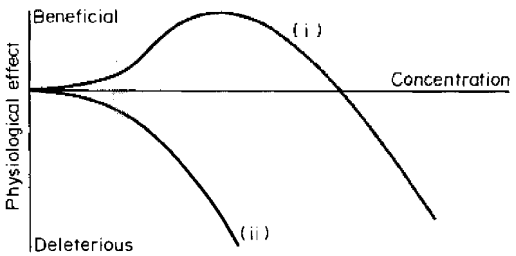


Figure 1 Physiological effect of (i) essential and (ii) toxic elements (reproduced with kind permission from Williams, ref. 3)

Table 1 shows the chronolgical discovery of the essentiality of the trace elements for maintenance of health in humans.[28–30] Deficiencies in trace elements are widespread geographically. Iron deficiency in anemia is the most common deficiency and is present in up to 90% of women in some areas. Iodine deficiency in goiter has been recognized for over 100 years; there are 'goiter belts' in the United States, and in the United Kingdom goiter was known as 'Derbyshire neck'. Deficiency in zinc leading to growth retardation, widespread in the Middle East, was discovered much later. Deficiencies in selenium, associated with cardiomyopathy and with higher incidence of some cancers, in fluorine, contributing to poor dental health, and to a lesser extent in copper and chromium also occur. Specific widespread deficiencies for the newer essential elements Ni, V and Si have not yet been found in humans (although they have been noted in animals; recently, V has been found to produce the same effect as insulin in diabetic animals). The requirements, however, for these and Mn appear to be much less than the amounts in usual dietary intakes.

Table 1 Chronological Order of Discovery of Essentiality of Trace Elements[a]

Fe	17th century
I	1850
Cu	1928
Mn, Zn, Co	1931–1935
Mo, Se, Cr	1953, 1957, 1959
Sn, V, F, Si	1970–1972
Ni, As	1974, 1975
Li, Br, Cd, Pb	Essentiality not proved

[a] Compiled from refs. 28, 29 and 30.

Deficiency syndromes of Zn, Cu, Cr, Se and Mo have occurred in patients on total parenteral nutrition (TPN). There is still much research to be done in assessing the nutritional status of many elements and understanding their metabolism, so that normal dietary intake may be supplemented for health benefits. Table 2 is a summary of the amounts required, the functions and the nutritional (usually dietary) imbalances in humans, where known, of the essential trace elements.[31–33] (Note that this summary does not attempt to include imbalances related to environmental toxicology and occupational hazards.) Several trace elements have important functions in the immune system. Some are associated with nucleic acid. Others have structural roles, such as Si in cartilage, F and Zn in bone. They may be parts of vitamins, such as Co in vitamin B_{12}, or hormones, such as iodine in thyroid hormones. Zn and Cr have a role in the synthesis and action of insulin.[31–33]

We shall discuss in greater detail four of the essential trace metals, namely iron, zinc, copper and cobalt, with respect to dietary deficiencies and remedies. The first three are present in the adult human body in the largest amounts and deficiency states are well known; cobalt is unusual, like iodine, in having a single known specific function. There are a number of interesting, general references which serve as a good starting point for the reader.[28–40] Several works devoted to specific elements not discussed in detail here are available, namely magnesium,[41] calcium,[42] chromium[43,44] and selenium.[45] The books by Underwood[33] and Bowen[46] are particularly thorough reference works; references 47–51 are invaluable for iron as well as other trace elements.

Table 2 Amounts and Functions of Essential Trace Elements in Man[a]

Element	*Amount in adult body*	*Recommended daily intake*	*Functions*	*Dietary imbalance*	
				Deficiency	*Excess*
Iron	3–5 g	10 mg (males) 18 mg (females)	Electron transport (cytochromes), oxygen carrier (haemoglobin), storage/transport (ferritin), enzymes, immune system	Widespread geographically; fatigue, anemia	Danger in hemochromatosis, Cooley's anemia, acute poisoning, Bantu siderosis
Zinc	2–3 g	15 mg	> 160 enzymes in main metabolic pathways, nucleic acid and protein synthesis, immune system	Occurs in Iran, Egypt; TPN, genetic disease, traumatic stress; growth depression, delayed sexual maturation, skin lesions, depression of immunocompetence, change of taste acuity	Unlikely except from prolonged therapeutic use; can interfere with Fe and Cu metabolism
Fluorine	3 g	1.5–4 mg	Structure of teeth, bones	Dental caries, possibly osteoporosis	Dental fluorides; severe fluorosis in parts of India and South Africa
Silicon	2–3 g	—	Calcification, structure of connective tissues	Unknown	Unknown
Manganese	1 g	2.5–5 mg	Enzymes in protein and energy metabolism, superoxide dismutase, mucopolysaccharides synthesis	Unknown	Toxicity by inhalation
Copper	80 mg	2–3 mg	Metal storage/transport (ceruloplasmin); enzymes in synthesis of cartilage, bone, myelin; interaction with iron	Occurs in malnutrition, TPN; anemia, neutropenia, skeletal and neurological defects	Danger in Wilson's disease
Vanadium	15 mg	—	Lipid metabolism, regulation of cholesterol synthesis, ATPases	Unknown	Unknown
Iodine	11 mg	150 μg	Synthesis of thyroid hormones	Goiter ('Derbyshire neck' in the UK)	May lead to thyrotoxicosis
Molybdenum	10 mg	150–500 μg	In metalloenzymes; xanthine, aldehyde, sulfite oxidases	Faulty metabolism of xanthine, sulfur	Gout-like syndrome in parts of Soviet Union
Selenium	6–12 mg	50–200 μg	Glutathione peroxidase, interaction with heavy metals; inhibitory effect on cancer	Endemic cardiomyopathy, conditioned by Se deficiency; muscle weakness	Known in parts of China
Nickel	10 mg	—	Interaction with iron absorption, nucleic acid, lipid metabolism	Unknown	Unknown[b]
Chromium	2 mg	50–200 μg	Potentiation of insulin, maintenance of normal glucose tolerance	In malnutrition, aging, TPN; impaired glucose tolerance, relative insulin resistance, elevated serum lipids, peripheral neuropathy	Unknown[b]
Cobalt	1–5 mg	3 μg Vitamin B_{12}	Part of Vitamin B_{12}, erythropoiesis	Vitamin B_{12} deficiency only, because of diet or failure to absorb	Unknown
Arsenic	1–2 mg	—	Iron metabolism	Unknown	Unknown[b]

[a] Compiled from refs. 31, 32 and 33.
[b] Except that dermatitis hypersensitivity and carcinogeneses because of excess exposure are well-known in environmental toxicology.

62.2.2.4.2 Iron

An extensive survey of the historical uses of iron with many original references has been given by Fairbanks *et al.*[47] Ancient civilizations called iron 'the metal of heaven', probably because of the relatively high amount in meteorites. Remedies containing iron have been known since 1500 B.C., two being mentioned in the Ebers Papyrus, an Egyptian pharmacopoeia and the oldest surviving manuscript of mankind. One was a recipe for a paste to be applied for pterygium, and the second, quoted here, was a relief for baldness:

'" O shining One, thou who hoverest above!
O Xare! O disc of the sun!
O protector of the divine Neb-Apt!"
to be spoken over
Iron
Red lead
Onions
Alabaster
Honey
make into one and give against.'

Another early example of iron usage is entirely legendary. Prince Iphyclus of Thessaly was unable to beget a child, and the seer-physician Melampus cured him. As a child, the prince had been frightened by his father wielding a bloody knife to geld rams. The father had driven the knife into an oak tree, where over the years it became completely buried. Melampus had the prince cut down the tree, recover the knife, scrape the rust from the blade into wine, and drink the iron-fortified liquor. The prince soon regained his potency. This appears to be the first reference in Western literature to both castration complex and medicinal use of iron.

Pliny the Elder wrote extensively on iron. It seems to have been a theraputic panacea for the Roman era. 1000 years later ibn-Sina catalogued the known 10th century anatomy, physiology and pharamacology in his 'Canon of Medicine'. The description of the uses of iron for a variety of problems ends with 'it restores sexual potency and strength to men', echoing the legend of Iphyclus.

The ancient physicians were remarkable in guessing that iron is the source of the colour of blood. In the 17th century, chlorosis was recognized. Sydenham in 1681 is credited with a remedy, '...a syrup made by steeping iron or steel filings in cold Rhenish wine...'. Not until the first part of the 18th century was the ash of blood shown to contain iron. In the 19th century the association of chlorosis with iron deficiency and the value of large doses of iron(II) salts were shown.[47] The last 100 years have shown rapid advancement in our understanding of iron absorption and metabolism. The incorporation of inorganic iron into hemoglobin was demonstrated in 1932. In the 1920s it was established that iron is important in the oxidative mechanisms of all living cells. Iron is present in simple iron proteins (ferredoxins), hemoproteins (hemoglobin and myoglobin), the oxygen carriers; cytochromes, the electron-transfer proteins, which function as reversible acceptors–donors of electrons; iron–sulfur proteins such as xanthine oxidase; iron-binding proteins involved in transport of iron such as transferrin and lactoferrin; the iron-storage proteins, ferritin, found in all cells; and hemosiderin, which seems to be deposits of ferritin.

Simple iron-deficiency anemia is our single most important nutritional disease, and probably the most common organic disorder seen in clinical medicine. Deficiency is accompanied by fatigue, palpitation on exertion, sore tongue, tinnitus, headaches, cold hands and feet, 'spoon nails', decreased resistance to infection, dysphagia, GI disturbances, angina and other symptoms. Even in patients with classic migraine headaches, treatment for iron deficiency may decrease the frequency of attacks. More rarely, iron deficiency may give rise to neurological symptoms simulating intracranial tumors, accompanied by increased cerebrospinal fluid pressure. Deficiency of zinc often occurs at the same time as iron deficiency. Causes include chronic blood loss, such as from menorrhagia, ulcers, malignancy or infections. Competition exists for growth-essential iron between bacterial, fungal and protozoan pathogens and their vertebrate hosts. The more virulent microorganisms can overcome the host's ability to withhold iron. Human requirement for iron is highest in the first 2 years of life, during the rapid growth of adolescence, and through the childbearing years for women, when absorption of approximately 2.0 mg d^{-1} is needed.

The concepts of iron deficiency and anemia, implying varying degrees of depletion of iron stores and of enzymes, and reduction of levels of circulating hemoglobin, are well understood. Clinical manifestations and diagnostic studies are thoroughly reviewed by Fairbanks *et al.*[47] In summary, in severe iron-deficiency anemia, in addition to morphologic changes in erythrocytes, some laboratory findings are abnormal: plasma iron concentration is low, total iron-binding capacity (TIBC) of plasma is often increased; transferrin saturation is usually $< 18\%$ and often $< 10\%$; and serum copper concentration is high, amongst others.

For mild anemia, the determination of red cell indices has some value in diagnosis; however, it should be realized that these indices may appear to be entirely normal and that they are subject to errors. Patients with 'statistically normal' hemoglobin values may show a positive hemoglobin response to iron therapy. A woman with hemoglobin concentration of 13g $(100\ ml)^{-1}$ may be iron deficient through excessive menstrual flow; for her a hemoglobin concentration of 15g $(100\ ml)^{-1}$

may be 'normal' in the physiological sense. Thus, the diagnosis of anemia based on arbitrarily selected criteria such as hemoglobin levels is unsatisfactory. A better criterion is the change in hematocrit value achieved by administration of oral iron(II) fumarate (60 mg Fe daily for 3 months). Studies using a correlation between this change and initial hematocrit value showed deficiency in 10–24% of the female population of Sweden. Put another way, the probability of iron deficiency is 100% for a hematocrit of <31%, falling to 28% and 3.2% at hematocrits of 37% and 40% respectively. A hematocrit value of >37.5% suggests a healthy iron level. There is still a real need for a better, simple, reliable method for detection of mild iron-deficiency anemia, a deficiency so common that it can almost be assumed to exist. The evidence of iron deficiency is often disarmingly vague.

Anemia may result from other complications even when iron supply is sufficient. A decrease in hemoglobin synthesis, a fault in transport mechanisms or destruction of erythrocytes have all been noted. Sideroblastic or iron-loading anemias are characterized by a fault in iron metabolism (see Section 62.2.3.2). There are also several other syndromes of iron deficiency known clinically, including pica and Goodpasture's syndrome (an immune-related lung and kidney disease). The different categories of anemia have been discussed in detail by Prasad.[48]

Oral contraceptive drugs have been shown to have a significant effect on iron metabolism. Serum iron and total iron binding capacity (TIBC) are consistently elevated. Hemoglobin is either unchanged or slightly altered. Both increases and decreases have been reported, but the number of subjects is small. (In pregnancy, a decrease is generally observed.) Serum copper and ceruloplasmin are also consistently elevated in these drug users, probably because of the estrogen component, whereas serum and plasma zinc are decreased. These copper and zinc levels are often inversely related, so that depressed serum zinc concentration may be a result of increased copper.

The richest dietary sources of total iron are organ meats (liver and kidney), egg yolk, dried legumes, corn, molasses and parsley. Liver is particularly valuable because of the high absorbability of its iron. However, only about 10% of dietary iron is absorbed. Iron deficiency anemia can be treated with soluble iron(II) compounds providing 200 mg in three or four daily divided doses. Oral iron(II) sulfate is the least expensive and is in wide use. Ascorbic acid increases the absorption efficiency of iron(II) sulfate. Parenteral administration of iron is used when oral iron is ineffective. Iron–dextran, a colloid formed from iron(III) chloride and an alkali-modified dextran, is one of several preparations available which has found extensive clinical use. It contains up to 28% Fe by weight and has a structural similarity to ferritin. Transfusion therapy may also be used in severe chronic anemia or acute hemorrhage.

Acute iron poisoning is also relevant to the discussion of therapy. Toxic effects of iron were recognized in 14th century Italy: 'He to whom has been given the magnetic stone... will become lunatic, melancholy, or furiously mad. Now the treatment is... fragments of emeralds and gold filings... with wine, and he is to be clystered with the milk of ewes and oil of sweet almonds.'[47] Nowadays, it is the combination of curious toddlers and bottles of attractive tablets that leads to most cases of iron poisoning. Two tablets (0.6 g) caused severe symptoms and 2 g have led to death. Symptoms of bleeding, gastoenteritis, shock and possibly coma may occur. Treatment consists of gastric lavage with 1% sodium bicarbonate solution followed by stomach instillation of 5 g desferrioxamine. In addition, an intramuscular dose of desferrioxamine (1 g, children; 2 g, adults) should be given.[49]

62.2.2.4.3 Zinc

Zinc is recognized as an essential element for normal function in all forms of life. Its deficiency can lead to various disorders including impairment of the following processes: protein and carbohydrate metabolism, capacity for learning, reproductive maturation and function, bone development and normal growth. Low zinc levels may result in mental lethargy and depression. Zinc is believed to be effective therapeutically in wound healing (*e.g.* following surgery) and in treatment of atherosclerosis. Zinc appears to have a role in DNA replication and transcription, as well as in protein synthesis.

In 1940 carbonic anhydrase was isolated from mammalian erythrocytes; the protein was shown to contain 0.33% zinc. In 1955 carboxypeptidase became the second zinc enzyme to be reported. About 20 zinc metalloenzymes have since been studied in great detail, and about 60–70 await complete characterization.

The numerous causes of human zinc deficiency, and conditions in which it exists, have been summarized by Prasad.[50,52] They include nutrition (inadequate diet), excessive alcohol ingestion, liver disease, gastrointestinal disorders (such as Crohn's disease), neoplastic diseases (conditioned

deficiency), burns and skin disorders (excessive losses of zinc), chronic disease and chronic renal failure. Acute zinc deficiency in Middle Eastern countries is probably a result of high phytic acid content of cereals. Additional zinc is required during normal pregnancy. Iatrogenic zinc deficiency may follow use of chelating agents, antimetabolites, antianabolic drugs and diuretics; use of total parenteral nutrition fluids omitting zinc; and use of penicillamine for Wilson's disease. Two genetic disorders are helped by zinc therapy. (i) Acrodermatitis enteropathica is a lethal, recessive trait disorder which develops in the first few months of life, in which dermatological, ophthalmic, gastrointestinal and neuropsychiatric problems are exhibited. Zinc supplements can result in complete cure. (ii) Sickle cell anemia patients exhibit many of the same clinical features as zinc-deficient patients, including delayed growth and delayed onset of puberty. This disease and its therapy are areas for further work.

In addition to the classical symptoms of zinc deficiency mentioned above, the following unusual conditions have been reported: liver and spleen enlargement, abnormal dark adaptation and abnormalities of taste. Several laboratory procedures for diagnosing zinc deficiency are available. Measurement of zinc levels in plasma is useful in certain cases. Levels of zinc in the red cells and hair may be used for assessment of body zinc status. More accurate and useful parameters are neutrophil zinc determination and quantitative assay of alkaline phosphatase activity in neutrophils. Determination of zinc in 24 h urine may help diagnose deficiency if sickle cell disease, chronic renal disease and liver cirrhosis are ruled out. A metabolic balance study may clearly distinguish zinc-deficient subjects.

The pharmacological use of zinc (use other than for zinc deficiency) is, with one notable exception, very recent. The use of topical zinc to promote healing of wounds (zinc oxide in calamine) has been known since 1550 B.C.[53] Recent studies report enhanced healing from oral zinc therapy for pilonidal cysts, venous stasis leg ulcers, major burns, leg ulcers in sickle cell anemia, and a variety of types of chronic wounds. The standard dose is 220 mg zinc sulfate (50 mg elemental Zn) given three times a day with meals. While this is a pharmacological dose of zinc (150mg d^{-1}), enhanced healing only occurs until the zinc level is raised to the normal physiological level, so that this is really an example of therapy for a deficiency. This effect is consistent with the fact that zinc is required for collagen synthesis. Zinc therapy has enhanced graft acceptance in children with major burns. Measurements of skin zinc levels in chronic steroid-treated patients are amongst the lowest observed. The effect of various stressors, including steroids, other drugs and radiation, needs to be studied. Anesthesia as well as surgical injury causes zinc levels to fall. Studies to determine if supplemental zinc will increase myocardial concentrations or will have a positive effect on the healing of infarctions have been suggested.[34]

Other diseases which respond to zinc therapy include sickle cell anemia and rheumatoid arthritis. Sickle cell anemia was the first condition to be described as a molecular disease. An *in vivo* antisickling effect with zinc therapy was demonstrated in 1977. The proposed mechanism is one of inhibition of calmodulin function by zinc. Only about 10% of administered zinc is absorbed and the therapy would be more effective if plasma zinc levels could be increased. The observations that rheumatoid arthritis (RA) patients (i) may often be zinc deficient, (ii) have low serum histidine levels, and (iii) often benefit from the drug D-penicillamine (a chelating agent which may enhance zinc absorption) and also that zinc has an antiinflammatory effect, have led to a study of zinc sulfate therapy for RA. Significant improvement in joint swelling, tenderness and morning stiffness was found. Brewer suggests that further clinical studies in this area are warranted, and, moreover, that a variety of inflammatory diseases (*e.g.* ulcerative colitis) might be successfully treated with zinc.[53] D-Penicillamine treatment for Wilson's disease has led to zinc deficiency manifested as severe skin lesions, hair loss and other problems persisting for several years. The lesions were reversible by zinc acetate therapy within one month.[50]

Zinc absorption is inhibited by most food and the elevated plasma level lasts only 5 h after a dose; thus it is better given five or six times a day, 1 h before or after meals. Zinc acetate may be better tolerated than the sulfate salt. Brewer prefers 25 mg elemental zinc, administered as the acetate, five or six times a day.[53] Zinc is relatively non-toxic as a drug. If more than 1 g zinc is ingested in a single dose, toxic symptoms such as abdominal pain, nausea, vomiting, fever, drowsiness and lethargy may occur. A more significant toxicity problem is zinc-induced copper deficiency which can be corrected with a supplement of 0.5 mg of copper as copper sulfate per day.[53]

62.2.2.4.4 Copper

Copper is the third most abundant heavy metal in the human body, the concentration being 1.4–2.1 mg per kg body weight. All tissues of the body require copper for normal metabolism.

Copper may be stored in the liver and released, as required, in the form of ceruloplasmin, for example. Like other trace elements, trace amounts of copper are essential for life, and excess amounts are toxic.

Copper is an essential component of numerous key metalloenzymes which are critical in melanin formation, myelin formation and crosslinking of collagen and elastin. Copper plays a vital role in hemopoiesis, maintenance of vascular and skeletal integrity, and structure and function of the nervous system. Thus a deficiency of copper can lead to a variety of adverse effects such as increased fragility in bones, aneurysm formation in arteries and a loss of lysyl oxidase activity in cartilage.[54–57] Articles on copper also appear in Sigel[1], volumes 3 and 5, all of volumes 12 and 13, and volume 14.

The causes of human copper deficiency include: (1) low intake – malnutrition, total parenteral nutrition (TPN); (2) high loss – cystic fibrosis, nephrotic syndromes; and (3) genetic factors – Menkes' disease. Copper deficiency may also be associated with chronic malabsorption, a situation which is made much worse in cases of gastric and bowel resection. Several special diets, including powdered milk, liquid protein and standard hospital diets are a means of inducing copper deficiency. The amount of copper in US food has decreased steadily since 1942, and may be related to the rising incidence of coronary artery disease. A copper deficiency may also occur as the result of the use of chelators for other purposes: for example, diethyl dithiocarbamate is an *in vivo* metabolite of ANTABUSE™ (disulfiram).

For the most part, adequate copper is received in diet and widespread human deficiencies do not occur, but deficiencies may arise because of antagonists. The metals Cd, Hg, Ag and Zn interfere with copper metabolism, probably by competing for copper-binding sites in proteins. Ascorbic acid depresses intestinal absorption of copper[56] (in contrast to iron). Some proteins in the diet adversely affect utilization of copper. The sulfide ion is a well known inhibitor of copper absorption, since it forms copper(II) sulfide which is insoluble.[56]

Like zinc, copper and its compounds have been used since ancient times, with copper dust, acetate, sulfate and carbonate reported in Egyptian and Hindu prescriptions, and also used by Hippocrates and Galen. Copper arsenite was used in 1892 for anemia and debility. Copper sulfate was recommended to strengthen man, to stimulate the heart and blood vessels, to increase deposition of fat and to treat anemia. The adult requirement is 1.25 mg Cu d^{-1}, about one third of which is absorbed. TPN should be supplemented with 0.5–1.5 mg d^{-1} (adults) and 20 μg (kg weight)$^{-1}$ d^{-1} (children).

Two genetic disorders of copper metabolism, Wilson's disease (see Section 62.2.3.3) and Menkes' disease, are known. The latter involves impaired intestinal absorption of copper[56,57] as well as probably subcellular metabolic defects which result in copper deficiency with respect to metalloenzyme activity. The characteristic 'steely' hair in Menkes' disease results from free SH bonds in hair protein because of failure of lysyl oxidase to produce the disulfide links. Depigmentation of hair and skin, hypothermia, cerebral degeneration, central nervous system retardation, skeletal demineralization and arterial degeneration are all seen. Copper supplements may benefit hypothermia and increase pigmentation but the disease is not generally cured.

A Cu^{II}–L-His_2 complex has been used in treating Menkes' disease, in a dose of 200 μg Cu (10 kg body weight)$^{-1}$, injected subcutaneously in 1 ml saline, pH 7.35. This complex has the advantage of resembling the form in which copper is transported in the blood serum and may prove to be more effective than simple copper salts.[56] Serum copper is increased in leukemia, Hodgkin's disease, various anemias, 'collagen' disorders, hemochromatosis, and myocardial infarction. Measurement of serum copper level together with other clinical parameters appears to be a useful index for evaluating disease activity and response to therapy in malignant lymphomas.[54]

62.2.2.4.5 Cobalt

Cobalt is rare on the earth's surface, but is found in fertile soil and in plants. It is required in the human body in the form of vitamin B_{12} (cyanocobalamin).

Vitamin B_{12} was the first metallo complex in living systems to be studied in great depth.[33,34,55] It is needed in the formation of hemoglobin, and the adult human body contains 2–5 mg of vitamin B_{12} and its derivatives. The stomach secretes a glycoprotein called intrinsic factor, which binds cobalamin in the intestinal lumen. Pernicious anemia is caused by a deficiency of intrinsic factor, leading to impaired absorption of cobalamin. A significant amount of research has centred on the preparation and investigation of model complexes containing cobalt. Co^{2+} can be substituted for Zn^{2+} in a number of enzymes without a gross change in activity, and has therefore been used as a probe of active enzyme sites.

Cobalt must be supplied in the diet in its physiologically active form, vitamin B_{12}. GI absorption of cobalt is about 25%, with wide individual variation; excretion occurs mainly *via* the urine. The major part is excreted within days and the rest has a biological half-life of about two years. Originally, the therapy for pernicious anemia was to have patients eat large amounts of liver. The most reliable treatment now is monthly injections of cobalamin.

Toxic levels of Co have occurred when addition of cobalt to beer caused cardiomyopathy in heavy beer drinkers. Industrial exposure has lead to pneumoconiosis and other pulmonary problems.

Model reactions have contributed significantly to our understanding of biological processes. Both pyridoxal phosphate (vitamin B_6) and B_{12}-coenzymes have proved useful in mechanism studies. Methyl transfer reactions to various metals are of environmental significance. In 1968 it was shown that methylcobalamin could transfer a methyl carbanion to mercury(II) salts in aqueous solutions. Recent research on interaction between B_{12}-coenzymes and platinum salts has shown that charged Pt^{II} salts labilize the Co—C bond. Secondly, the B_{12}-coenzymes are unstable in the presence of platinum salts; this observation correlates with the fact that patients who have received *cis*-platin develop pernicious anemia.

62.2.3 THERAPEUTIC USES OF LIGANDS WHICH FORM COORDINATION COMPLEXES

62.2.3.1 Chelation Therapy in Heavy Metal Poisoning

The mechanisms of metal ion poisoning may be grouped into two classifications: (i) electrolyte imbalance, absorption of negative sites of enzymes and osmotic imbalance, which occur in Li^+, Na^+, K^+ and Ba^{2+} (type a metal ions) poisoning; and (ii) complex formation with toxicity related to the strength of the complex bond, which occurs for all other metal ions. The subject of electrolyte imbalance will be referred to again in the last section of this chapter. Type b metal ions (those which form stronger coordinate bonds to sulfur than to oxygen) tend to accumulate in the kidneys and liver. Nephrotic syndrome, or kidney failure, is the common toxic action.

Therapeutic chelating agents are compounds used as antidotes for metal poisoning. Several reviews on the subject have been published in a work edited by Martell,[18] as well as in books.[58,59] There is rapid reaction of an agent with a metal bound to a biological site; the resulting binary or ternary complex involves the metal ion, the agent and possibly another ligand, and it is water soluble. The usual route of excretion is from the bloodstream to the kidney, to the urine, where elevated metal concentration is confirmed by analyses. Excretion *via* the liver, bile and feces is also an important route for some metals such as copper and iron.[58–60]

Because time is critical in cases of acute metal poisoning, there may be a high rate of transport of heavy metal complexes leading to kidney damage, so that dialysis may be necessary. When treatment is begun too late, damage may be irreversible. The ideal agent would be specific for a given toxic metal, since it would likely have less tendency to alter the balance of other essential metals. Other requirements of chelating agents are that they should: possess an $LD_{50} > 400$ mg kg^{-1}; form highly stable complexes with the metal ion to be removed — five- or six-membered chelate rings are usually the strongest, and a ligand that can form two or more rings will produce an even more stable complex; have a high water solubility; form complexes that are water soluble; form complexes that are not more poisonous than the metal ion; permit resulting complexes to be excreted *via* the kidneys without causing further damage; and not undergo significant metabolism. For chelating agents which can be metabolized, a high toxicity is often associated with a high lipid solubility, which permits the metal complexes to enter the brain. Steric aspects should be considered: Ag(I) and Au(I) prefer two linear bonds, which are best achieved by eight-membered rings or by two monodentate ligands, and these ions will not form five-membered chelate rings.

The first chelating agent to be used effectively in humans as a metal poisoning antidote was 2,3-dimercaptopropanol-1 or BAL (British Anti-Lewisite). See Table 3 for abbreviations and chemical names of chelating agents. BAL was originally developed to protect —SH enzymes in the body from arsenicals in war gases. It protects such enzymes from several metals in various oxidation states, including V^{II-V}, $Au^{I/III}$, Cd^{II}, Hg^{II}, Pb^{II}, Sb^{III} and Bi^{III} as well as As^{III} ion poisoning. The chelates formed are sufficiently water soluble to be excreted in the urine.

BAL is lipid soluble and it has the ability to remove metal deposits not available to attack by other chelators. More effective and less toxic compounds have since become available; these include vicinal dithiols, other dithiols, aminocarboxylic acids, cysteine derivatives, and others. Unithiol (sodium 2,3-dimercaptopropane-1-sulfonate; DMPS) forms very stable, water soluble complexes with Hg^{2+}, Pb^{2+}, Cd^{2+}, Zn^{2+}, Bi^{3+}, As^{3+}, Sb^{2+} and Ni^{2+}. The complexes are nearly all less toxic than

Table 3 Chelating Agents: Abbreviations and Chemical Names[60]

BAL	2,3-Dimercaptopropanol-1, British anti-Lewisite or dimercaprol
DCBM	Dithiocarbamate
DFOA	Desferrioxamine-B, DESFERAL™
DMPS	Sodium 2,3-dimercaptopropane-1-sulfonate, Unithiol
DMSA	2,3-Dimercaptosuccinic acid
DPA	D-(−)-Penicillamine
DTPA	Diethylenetriaminepentaacetic acid
EDDHA	Ethylenebis-*N,N'*-(2-*O*-hydroxyphenyl)glycine; also EHPG
EDTA	Ethylenediaminetetraacetic acid
TETA	Triethylenetetramine

the metal ions alone (except Zn and Cd with BAL), and are excreted *via* the urine with a half-life of approximately 2 h. 2,3-Dimercaptosuccinic acid (DMSA) is much more soluble in water and much less toxic than BAL, can be given orally and is less expensive than DMPS, and it is an effective antidote for the same range of metals. It has also been used, as the antimony complex, in treating schistosomiasis. For Pb poisoning it is as effective as Ca EDTA. It is capable of enhancing methyl mercury excretion from the brain. Other dithiols, including glucosides of BAL and structurally related sulfonate-containing compounds, have been studied.

Hundreds of aminopolycarboxylic acids have been prepared. They all contain the $=N—C—CO_2H$ entity which gives very stable five-membered ring chelates when N and O are bonded to the same metal ion. Na_2Ca EDTA was first used as an antidote for lead poisoning and has since been studied for other metals such as the radioactive lanthanides and the actinides. Diethylenetriaminepentaacetic acid (DTPA) is frequently more effective than EDTA because its complexes have higher stability constants. The zinc complex Na_3Zn DTPA is the preferred agent for removing deposits of transuranium elements resulting from industrial exposure.

In D-penicillamine and cysteine derivatives, the three donor groups —SH, $—NH_2$ and $—CO_2H$ exist together (see Section 62.2.3.4 and also Chapter 20.2). This entity has wide general coordinating ability, and it chelates with many toxic metals. Cysteine itself is a naturally occurring amino acid and the human body enzyme systems can transform it rapidly. It may give temporary protection against heavy metals and then lose its antidotal action. Its derivative, D-penicillamine (DPA), with two methyl groups on the sulfhydryl carbon, has been found to be a valuable therapeutic chelating agent. It was first introduced by Walshe in 1956 for enhanced copper excretion in patients with Wilson's disease (see Section 62.2.3.3). It has been used for removal of Pb, Hg, Au, Pt compounds and Sb, as well as in treatment of rheumatoid arthritis. It can be administered orally, has little inherent toxicity, and is readily available. It seems to be replacing BAL in the treatment of heavy metal poisoning. Acetylation of penicillamine removes the donor properties of the N atom, but the resulting compound penetrates cell membranes more easily. Thus *N*-acetyl-D-penicillamine can remove Hg in methyl mercury from brain tissue more effectively than DPA and is used for chronic mercury intoxication.

A group of ligands known as dithiocarbamates are finding use in treatment of nickel poisoning from exposure to $Ni(CO)_4$ in industrial settings.[60]

62.2.3.2 Iron Overload

Cooley's anemia is a lethal hereditary disease in which there is a fault in hemoglobin synthesis. This condition is reviewed in four articles in a book edited by Martell.[18] The patients must receive blood transfusions starting at age six months and continuing every 3–4 weeks for the rest of their lives. The increased iron input from these transfusions exceeds the capacity of ferritin and transferrin, and results in severe iron overload with iron deposits in the heart, liver, endocrine glands and other organs, usually leading to death before age 20. Iron chelation therapy has been used since the 1960s to retard the condition. Desferrioxamine or DESFERAL™ has proved relatively successful and is now widely used for iron chelation therapy. Desferrioxamines are naturally occurring, selective iron(III) chelators isolated from actinomycetes. The drug form is subject to a combination of metabolic destruction and rapid excretion. It has moderate toxicity and can also be used as an antidote for iron poisoning. Use of ascorbic acid with the drug enhances the amount of iron removed. It is not an ideal drug because it must be injected, is very expensive ($1000 patient^{-1} month^{-1}) and is only effective when the iron load is ten times the normal level. Research has concentrated on development of more effective iron chelators.

The ideal chelator should be inexpensive, capable of being administered orally and free of side effects. It should have a selective ability to bind Fe^{III} rapidly, relative to ferritin and transferrin,

and should not interfere with hemoglobin, myoglobin and the cytochromes, or with the normal biochemical processes. With a knowledge of bacterial iron chelators and the techniques of modern chemistry, it is becoming possible to synthesize molecules that are more effective than the natural substance in DESFERAL™ in removing iron from tissues.

In general, ligands which have a high selectivity affinity for Fe^{III} (high effective stability constant *in vivo*) should be polydentate and relatively acidic oxy-donors, such as derivatives of catechol, 8-hydroxyquinoline, hydroxamic acid and carboxylic acids. Over 100 such agents have been evaluated for clinical use. Extensive tests with ethylene-*N,N'*-bis-2-(*O*-hydroxyphenyl)glycine (EHPG) suggest potential improvement over DESFERAL™. The design of new hexadentate ligands, especially cryptates, is important in finding a source of more effective chelators. Many of these chelates resemble analogous compounds used by bacteria to chelate iron.

The coordination chemistry and distribution of plutonium in the body is similar to that of iron and desferrioxamine can mobilize ^{239}Pu from most of the organs. This fact makes the drug important for safety in the nuclear industry.

An intake of 25–75 mg Fe d^{-1} may be safe. Long term iron overload has been noted in South Africa (Bantu siderosis). Ingestion of up to 200 mg Fe d^{-1} may be the result of eating food cooked in iron pots or drinking Kaffir beer containing 15–120 mg Fe l^{-1}. Ethiopians have a high iron intake (up to 500 mg d^{-1}), but as siderosis is not common, much of this iron must be unavailable.[33] This type of hemosiderosis should be treated by preventative measures to restrict the amount of iron in the diet.[48]

62.2.3.3 Copper Removal in Wilson's Disease

Wilson's disease is the result of a genetic fault in metabolism, and is characterized by a reduced ceruloplasmin level, an excess of copper in the liver, progressive liver disease, neurological symptoms and the presence of Kayser–Fletcher (KF) rings in the eye. The disease is fatal without treatment. Removal of excess copper by treatment with the drug D-penicillamine, or with triethylenetetramine (TETA) for those who do not respond to D-penicillamine, has been successful. KF rings are always present in patients over 12 years old having Wilson's disease, and may be observed before other clinical abnormalities. The damage to various organs is caused by deposition of excessive amounts of copper. It is desirable to diagnose patients in the asymptomatic state, but this usually only happens when they are relatives of known patients. Any person having a ceruloplasmin level of less than 20 mg dl^{-1}, or more than 250 μg Cu per gram of dry liver, must be considered to have Wilson's disease. Chelation therapy was proposed by Cumings in 1948. BAL was used initially. In 1957, Walsh started D-penicillamine as an oral chelation therapy and it is still the treatment of choice. Treatment requires life-long administration of about 1 g daily, and such patients now have normal life expectancies. Only the pure D isomer should be used, as the L isomer is more toxic. Some patients become intolerant to D-penicillamine and may be treated effectively by TETA.[24] On treatment with D-penicillamine, neurological improvement may precede the disappearance of the KF ring, unless irreversible brain damage has occurred.[54] There is now evidence that D-penicillamine therapy should be supplemented with pyridoxine (vitamin B_6) and zinc acetate, and probably also with vitamin A, in order to minimize toxic side effects.

62.2.3.4 D-Penicillamine for Rheumatoid Arthritis

The mechanism of action of D-penicillamine as an antiarthritic drug is still unknown, but since we know penicillamine can form a variety of metal chelates and complexes, it seems appropriate to include a further note on it here. D-Penicillamine has become established through a number of double-blind controlled clinical trials, as an efficacious agent for treatment of rheumatoid arthritis (RA). Amongst available second line agents it is being used as the drug of first choice about as frequently as MYOCHRISIN™ in Canada. Benefit is achieved in nearly 70% of patients, and about 30% of patients must discontinue because of adverse side effects. There is no increase in toxicity amongst the elderly. Our results indicate an acceptable efficacy at lower doses (500–600 mg d^{-1}). Only the pure D isomer is used in medicine, since the L and DL forms are toxic. We advocate a strict toxicity monitoring program, including full blood and urine analysis monthly.[61] Again, supplements of pyridoxine, zinc acetate and vitamin A may prove useful in reducing side effects.

62.2.3.5 Aluminum Removal in Alzheimer's Disease

Aluminum is the most common metal in the earth's crust, and it is perhaps surprising that its concentration in the human body is so low. About 50 mg Al d^{-1} is ingested in foods and dusts. The concentration of Al is relatively high in processed foods such as cheese and pickles, and in plants that thrive in acid soils such as cranberries and onions. Cooking of acidic foods in aluminum pots, addition of alum as a food preservative and the use of antiperspirants may contribute to increased Al levels in the human body. Antacids containing aluminum are common therapy for peptic ulcers. Normally the Al is eliminated and there is no resulting toxicity, but aluminum has a neurotoxic effect and its absorption from orally administered salts is a potential hazard. Patients undergoing dialysis because of renal failure are usually given about 4 g aluminum hydroxide gel daily. Such patients may develop dialysis dementia and may have a brain level of Al which is twelve times greater than controls.

Alzheimer's disease (AD) is the most prevalent form of senile dementia. Up to two million people in North America suffer from it, and it is the fourth cause of death in the elderly. The cause and treatment of this disease are therefore extremely important. Although the role of aluminum in AD and its *in vivo* chemistry is not known in detail, patients with Alzheimer's disease have been shown to have elevated aluminum concentrations in certain parts of the brain. Aluminum appears to concentrate in the nucleus. Crosslinks with DNA strands have been found. Crosslink formation can be reversed by sequestering the aluminum with EDTA.

Three associations between Down's syndrome and Alzheimer's disease have been noted. For Alzheimer's patients there is a higher frequency of Down's syndrome in the family tree. People having Down's syndrome who survive to age 30 or 40 often develop Alzheimer's disease at that time. In both diseases there are fingerprint abnormalities which may serve as markers. In Down's syndrome an abnormality in chromosome 21 has been identified, and the evidence suggests that there may be a different abnormality in the same chromosome for Alzheimer's disease.

A possible link between AD and the infectious prion (a particle smaller than the smallest virus) is being studied by some researchers.

Aluminum may be a compounding factor in AD; it may accelerate or alter the course of the disease *via* deregulation of calcium. Calmodulin (a protein with four binding sites) activates a number of enzymes and is an important messenger in brain cells. Al binds to this protein with ten times the affinity of Ca, and changes its conformation.

If it can be shown conclusively that Al removal alters the course of AD, then Al exposure should be regulated, and removal may be important. Desferrioxamine has been found to remove Fe and Al together in the ratio 5 Fe to 3 Al. The drug has the disadvantage of being very expensive (see Section 62.2.3.2). In a pilot study patients receiving desferrioxamine deteriorated less than the placebo group. The study is currently being continued with a larger group.[62]

AD is a primary degenerative dementia affecting humans as young as in their forties. The German physician Alois Alzheimer first described the disease in 1906. It is characterized by senile plaques and paired helical filaments (PHFs), and the severity of the condition directly parallels their number.[63] The involvement of aluminum in this and related dementias (dialysis encephalopathy and amyotrophic lateral sclerosis – Parkinson dementia in Guam) is currently a highly contested issue in neurological research.

Elevated levels of Al have been reported in some regions of the brains of subjects dying with AD.[64] The intracellular locus of Al accumulation is the nuclear chromatin in AD,[65,66] and the cytoplasm in dialysis brains.[67] The association of Al with the nuclei of brain cells has also been demonstrated in experimental animals with Al-induced encephalopathy.[68,69] Researchers agree that Al levels increase with human age; however, whether the levels are pathologically elevated in AD patients, or are just age associated, remains controversial.[70,71] It seems likely that there is a regulatory mechanism for Al in the human body, and that Al may be an essential element whose function has not yet been identified.

The main research problem is that Alzheimer-type neurofibrillary degeneration has not yet been reproduced in the laboratory. The Al ligands in the brain remain to be identified and the chemical steps in the formation of Al-containing tissue must be defined. A complicated concentration- and pH-dependent interaction between Al and DNA occurs *in vitro*[72,73] involving the formation of at least two Al–DNA complexes. The solution interactions of Al^{III} with calf thymus DNA[74] and ATP[75] have been studied with the resulting proposals that three distinguishable Al–DNA complexes and four Al–ATP complexes are formed. In the latter study, it was possible by ^{27}Al NMR to distinguish the varying degrees of binding of Al^{III} to the bases and phosphates of the nucleotide.

Clinically, the administration of desferrioxamine (DFO)[76] has been reported to increase urinary Al excretion in humans and to slow the progression of AD symptoms in a small number of patients.[77] Very recently, a major step in the diagnosis of AD was reported in the preparation of antibodies that specifically recognize PHFs in human brain tissue.[78] This may lead to a diagnostic test, which is a very pressing need because other conditions that cause dementia, such as depression and drug toxicity, are reversible. Also therapy for AD may be more effective if it is diagnosed early. Presently AD can only be confirmed on autopsy.

62.2.3.6 Antiviral Chemotherapy

At the present time, there is no accepted chelating agent which can be used against common influenza viruses in humans. A virus has a core of either DNA or RNA and a protective coat of many identical protein units. All viruses are either rods or spheres, that is the protein coats are cylindrical shells having helical symmetry or spherical shells having icosahedral symmetry. Viruses reproduce inside living cells, where each viral nucleic acid directs the synthesis of about 1000 fresh viruses. These are then released and the host cell may die.

Certain metal chelates have been found to act in an antiviral capacity by interfering with the viral cycle. The therapeutic substance may (i) destroy the virus outside the cell; (ii) occupy sites on the cell surface and prevent penetration by the virus; or (iii) prevent replication processes inside the cell. Current research is centred on understanding the molecular biology of viral infections and on finding substances with selective toxicity. Substances which are effective *in vitro* may not be so *in vivo*, where they must be soluble in body fluids, be transported to the site of the viral infection and be capable of blocking the viral cycle. Then too, they may exhibit a curare-like effect and therefore not be usable in therapy. To be effective, antiviral agents would have to be given before the peak of virus multiplication, and not be toxic. Symptoms caused by overreaction of the host immune system will not be relieved except by general supportive treatment (bed rest and acetaminophen). In spite of these limitations some antiviral drugs are known, and the relationships of their activity to steps in the viral cycle are discussed by Perrin and Stunzi.[79] Phosphonoacetic acid has shown activity against herpes viruses by inhibition of the virus DNA synthesis. Acetylacetone (2,4-pentanedione) derivatives are active against herpes simplex and some RNA viruses, including influenza. The role of metal ions in these mechanisms is being studied, for example by computer models of blood plasma. Cu, Zn, Mg, and Ca ions are believed to be important. Metal complexation in the biological activity of bleomycins is the subject of a review. 8-Hydroxyquinoline has been found to have antifungal and antibacterial properties in the presence of metal ions. Many other examples are known.

62.2.4 COMPOUNDS WHOSE INTERACTIONS *IN VIVO* ARE UNKNOWN

62.2.4.1 Electrolyte Balance

62.2.4.1.1 The role of Na^+, K^+, Mg^{2+} and Ca^{2+} ions

There are several labile elements for which the nature of the coordination sphere around the metal ion *in vivo* is somewhat speculative, and for which the amount of well-defined coordination chemisty in medical therapy is still rather small. These elements, Li, Na, K, Ca and Mg, are critical in several biological processes: they control osmotic balance in cells and the stability of intracellular structures such as nucleic acids.[55,80] Their release, transport and exchange trigger and regulate numerous biological actions. Na^+, K^+, Mg^{2+} and Ca^{2+} are abundant in living systems, reflecting the high natural abundance of these elements in the earth's crust and their ease of incorporation. Their distribution is selective, with K^+ and Mg^{2+} concentrated in cytoplasm, and Na^+ and Ca^{2+} concentrated outside cells. Intracellular K^+ concentration is 150 mM, 30 times higher than extracellular, whereas intracellular Na^+ is about 15 mM, 10 times lower than in extracellular fluids. Energy is required to maintain this cation gradient across the cell membrane, and this energy comes from the hydrolysis of ATP, which requires the enzyme adenosine triphosphatase (ATPase) and the various ions.

For a cell at rest, K^+ is pumped in and Na^+ is pumped out. (Perhaps up to one half of the basal metabolic rate in man (1700 kcal d^{-1}; 7100 kJ d^{-1}) is expended in pumping Na^+.) Localized reversals of this process coincide with control and trigger of electrical impulses: intracellular Na^+ level is particularly low in nerve and muscle so that entry of a small amount of Na^+ causes a large increase in concentration. The shock observed after severe burning is because K^+ ions are lost from within

cells. The use of these ions in therapy is concentrated on maintaining appropriate balances, for example the lowering of Na^+ to reduce hypertension.

Magnesium ions are found complexed with nucleic acids inside cells and are necessary for nerve impulse transmissions, for muscle contractions and for metabolism of carbohydrates. The physical integrity of the DNA helix is dependent on Mg^{2+}, and the physical size of RNA aggregates is controlled by Mg^{2+} concentrations. Magnesium deficiency may be asymptomatic; some symptoms include muscular twitching and tremors, vertigo, weakness, numbness; sweating and tachycardia; apathy, depression, poor memory and confusion. Increased Mg^{2+} in the diet has been claimed to reduce the extent and frequency of myocardial infarctions. Milk of magnesia and epsom salts ($MgSO_4 \cdot 7H_2O$) are used as laxatives. Overdoses of magnesium can cause depression and anasthesia. The use of magnesium-containing antacids such as magnesium oxide or trisilicate in patients with renal failure causes magnesium intoxication.[51]

Calcium, phosphorus and vitamin D are needed for formation of bones and teeth. Supplements containing calcium, fluoride and vitamin D are commonly used to treat osteoporosis, and some American physicians recommend 'Tums' as an inexpensive source of calcium. Calcium is needed also for formation of milk, maintaining correct heart rhythm, and conversion of fibrinogen into fibrin to form blood clots. Calcium salts are sometimes administered to promote blood clotting.

Calcium deficiency in blood plasma causes muscle cramps, twitching and eventually convulsions. If the blood calcium level falls, calcium is leached from the bones, causing osteomalacia. A group of cardioactive drugs known as the 'Ca antagonists' block influx of Ca^{2+} into infarcted, dying heart muscle cells following myocardial infarction.[55,80]

62.2.4.1.2 Lithium in psychiatry

The use of lithium in medicine has been the subject of recent reviews by Birch,[81] Birch and Sadler[29] and references therein, and Tosteson.[82] Historically, the use of lithium in medicine began with the treatment of 'gout and rheumatics' in 1859. For the following 90 years, lithium was proposed for a variety of disorders and then discarded; for example, lithium bromide was considered to be an effective sedative. In 1949 lithium was introduced into psychiatric practice and lithium carbonate, Li_2CO_3, became the first of the modern psychotropic drugs. In a review of double-blind trials Schou and Thomsen (1975) support the prophylactic use of this drug in bipolar (manic-depressive) illness.

About 0.1–0.2% of the general population are receiving lithium. About 50–60% of these patients are benefitting, if appropriately diagnosed. Daily dose depends on age, body weight and kidney efficiency; it is usually between 1 and 2 g Li_2CO_3 per day in divided doses. 'Slow release' preparations have been tried but not found to produce an advantage. The objective is to maintain plasma lithium level in the range 0.6–1.2 mmol l^{-1}. At levels greater than 2 mmol l^{-1} toxic symptoms such as skin rash, tremors, confusion and GI disturbances are likely to be seen. Li treatment is by nature a long-term process, and considerable supervision and monitoring are required. A Li saliva test which would correlate with the amount of Li circulating in the cerebrospinal fluid would be an advantage over the continual blood tests presently used for monitoring.

Long-term side effects of lithium treatment include weight gain. The treatment is associated with development of hypothyroidism in about 10–15% of cases. There is an association with kidney disease. Birch has expressed the general view that Li may interact with magnesium-dependent processes, and theoretical chemistry supports this view. Despite the widespread clinical significance of Li, there is presently no consensus on its mode of action. One postulate for the mechanism is termed 'hyperpolarization'. Li affects the conductivity in cell transport channels. Other explanations include modulation of neurotransmitter concentrations and inhibition of $Na^+/K^+/Mg^{2+}/Ca^{2+}$ ATPases.

Lithium has the smallest crystal radius but the largest hydrated radius of the alkali metals. Its high polarizing power gives it a high affinity for oxygen and nitrogen binding sites on ligands; in this respect it is most similar to magnesium. Since a great many biological processes are magnesium dependent, competition between Li and Mg could disturb a number of balances in biochemical reactions. Selective complexation on the basis of size of specific metal ions to facilitate the transport across membranes *in vivo* has been shown by such naturally occurring antibiotics as valinomycin (for potassium), and actinomycin (for sodium). A series of such ligands, called ionophores, can be produced, including crown ethers and cryptands, both of which are able to transport highly charged ions through lipid membranes. Such ligands do not occur naturally in man, but channels for transport of ions through membranes have specific diameters for specific ions. A study of

ionophores and their reactions may provide more information on lithium binding and action, which in turn may provide more knowledge of the mechanisms of psychoses.

The possibility of a relationship between depressive illness and cancer has been suggested. It should be realized, however, that the attributing of certain diseases to certain personality types has been common in the history of medicine (for example tuberculosis) and has proved to be proportional to ignorance of the true causes. There is a case review showing that patients having depressive illness have greater than average incidence of cancer; there is one prospective study in Iowa and one in Europe. A question which should be posed to and studied by psychiatrists in general is: 'What percentage of recurrent manic-depressive patients have cancer?' A related question which should be posed to oncologists in general is: 'What percentage of cancer patients are exhibiting manic-depressive illness?' How do we know if a patient has been appropriately diagnosed? It seems likely that cancer could produce sufficient metabolic changes in a person that depression or psychotic symptoms would be manifested. Also, a patient realizing that he may be terminally ill is very likely to feel hostility, repression and depression. If more simple screening tests for various carcinomas were available (*e.g.* blood tests, trace element concentrations), cancer patients could avoid being diagnosed as psychiatric patients, and physicians could avoid mistaken diagnoses.

62.2.4.2 Vitamins, Hormones and Miscellaneous Drugs

In addition to the well-defined inorganic complexes and potent chelating ligands already discussed, there are numerous substances — vitamins, hormones and drugs — which contain (i) heteroatoms capable of forming chelates, or chelating structures, in addition to other pharmacophoric groups; or (ii) donor sites which can form complexes but not chelates. For many of these substances, particularly those of group (ii), there is no clear correlation between effect or activity and metal affinity. In other words, the literature does not hold a body of well-defined coordination chemistry for all these substances. Nevertheless, some research is in progress. No chelating agent can be expected to be active physiologically unless its stability constants are at least as high as those of the common amino acids. Yet if the stability constants are too high, the substance will be saturated before it reaches the desired site of action. If cell penetration is desired, lipophilic groups are added to the molecule.[83]

The properties and modes of action of vitamins and hormones are the subjects of many volumes, including refs. 83–85, and will be mentioned only briefly here. Examples of such substances which have strong chelating properties are thyroxine, histamine, noradrenaline and adrenaline. In mammals, both a thyroid and a parathyroid hormone exist to regulate the level of circulating calcium. Calcium controls the permeability of semipermeable membranes and the excitability of the nerve cell membrane. Calcium ions play a role in release of neurotransmitters. In the catecholamines, all the metal binding occurs between the two oxygen atoms attached to the benzene ring.

Few attempts have been made to study formation of metal complexes by hallucinogenic drugs, but available data suggest that under physiological conditions there are no strong tendencies. Diazepam (a tranquilizer) binds to metals *via* nitrogen and forms well-defined complexes ML_2X_2, $M = Cu^{2+}$, or ML_3X_4, $M = Co^{2+}$, Ni^{2+}, $X = Cl^-$, Br^-, L = diazepam. Barbiturates form complexes with Co, Ag and Hg ions.[21]

62.2.4.3 Aging, Depression, Senility and Trace Elements

Much apparent senility in the elderly is really undiagnosed depression — at least 15% and likely as much as 35% or more. Obviously, investigations for depression should be made by physicians before assuming Alzheimer's disease or other conditions. We have seen in reviewing the essential trace elements and their deficiencies and excesses how important the levels of these elements are to general health and a feeling of well-being. There have been studies on trace element distribution which show considerable change with aging — accumulation in one organ and reduction in another. This whole area opens an exciting avenue of research into the relationship of the relative distributions of trace elements in various diseases.

62.2.4.4 Interactions Between Elements, Vitamins and Drugs

There is a danger of creating new imbalances by careless use of supplements of vitamins and trace minerals, hormones and drugs. Examples of interaction between trace elements and vitamins include the following: vitamin C (ascorbic acid) enhances the biological availability of iron, de-

presses that of copper, and renders selenium almost totally unavailable. Zinc is required for the function and metabolism of vitamin A.[31] There is a vitamin E-dependent role for selenium. Glutathione peroxidase (GSH-Px) was identified as a selenoprotein in 1973. Both vitamin E and Se protect membranes from oxidative degradation. It is believed that GSH-Px acts to destroy peroxides before they can attack cellular membranes, while vitamin E acts within the membrane itself preventing the chain reactive autoxidation of membrane lipids.[33,34,51]

62.2.4.5 Effect of Metals on Drug Absorption

Drug interactions can occur at many sites – at receptor or plasma protein binding sites, or in the liver and kidney. An important area for interaction is the site of drug absorption in the GI tract. Here a variety of factors, including changes in pH, various foods, antacids, and the formation of insoluble chelates and complexes, contribute to drug interactions. Considerable research has been done on the effects of metal salts or metal-containing antacids. A large number of drugs show decreased absorption because of magnesium or aluminum hydoxide gels (common antacid preparations). As an example, decreased tetracycline aborption results from interaction with Ca^{2+}, Fe^{2+}, Mg^{2+} and Al^{3+} to form poorly absorbed chelates: thus if iron salts and tetracycline are both prescribed they should be taken separately at 3 h intervals. A drug absorption interaction could cause unexpected therapeutic failure – non-prescribed medication, especially antacids, could be interacting with the prescribed drugs.[86]

62.2.5 STEREOSELECTIVE ACTIONS OF DRUGS

There is currently a growing awareness amongst pharmacologists of the importance of stereochemistry, particularly of the chirality of drug molecules. These drugs may be coordination complexes, ligand molecules with potential for *in vivo* coordination, or molecules whose *in vivo* interactions are unknown.

Stereoselectivity in the metal complexes of amino acids and dipeptides has been reviewed by Pettit and Hefford,[87] and will not be discussed further here.

Most clinicians will know only the generic of trade names of a drug. Few will know the chemical name or will be aware of the two-dimensional representation of the structure, and even fewer will understand the three-dimensional implications of that structure. A classic case of this was the early work by Hill *et al.*[88] on the anticancer activity of the platinum complexes dichloro(1,2-diaminocyclohexane)platinum(II). It was not realized that the 1,2-diaminocyclohexane ligand existed in three different forms and that the three derived platinum complexes might have different biological activities. Kidani and his colleagues[89] were the first to synthesize the three different isomers and to show there was a distinct difference in biological activity and therapeutic index. Investigation of the implications of chirality with respect to gold drugs is being carried out in our own research group.

Many of the drugs used in clinical practice are chiral, that is they exist in two structurally different forms, called enantiomers, which are mirror images and are related to one another in the way that the left hand is related to the right. Most of these drugs (over 80%) are administered as racemates (mixtures of the left- and right-handed enantiomers) because (i) the method of preparation produces a racemate and separation may be too costly, or (ii) in the case of a newly discovered drug the techniques for separation of the two forms may not yet be developed, or (iii) as quoted to us by a drug company scientist, 'one form is active, the other is not, and since we have to use a filler anyway there is no point in separating the two chiral forms'.

That the different chiral forms of a drug may have different biological and medical properties is hardly surprising. Many biological molecules are chiral and exist in living systems as one enantiomer only. Proteins are made up of only the L forms of amino acids. The normal forms of DNA (A and B) are right-handed helices. That a particular 'handed' enantiomer of one compound interacts differently with the two enantiomers of another compound has been known since the days of Pasteur.[90] This effect is often used as the basis of separation of enantiomers and can explain why the different enantiomers of a chiral drug have different biological and physiological activity. More importantly, however, the two isomers of a drug may follow different metabolic pathways, and pharmacological activity is often conferred by one isomer only. It has been suggested by Ariens[91] that the terms 'eutomer' and 'distomer' be used for the enantiomers with the higher and lower pharmacological activity. Obvious reasons for using the eutomer alone are (i) the distomer

is metabolized to toxic products, (ii) the distomer contributes to adverse side effects, (iii) the distomer is metabolized to products with unfavorable (*e.g.* too potent) pharmacological action, or (iv) the distomer counteracts the pharmacological action of the eutomer.

The drug thalidomide serves to illustrate the first of these points: with respect to hypnotic potency, the (*S*)-(−), (*R*)-(+) and (*RS*)-(±) racemate of thalidomide are all equally active, as tested by prolonging of sleep induced by phenobarbitol. (*S*)-(−)-Thalidomide, but not (*R*)-(+)-thalidomide, is transformed *in vivo* to L-*N*-phthaloylglutamine and L-*N*-phthaloylglutamic acid, products that are both embryotoxic and teratogenic in SWS mice and Natal rats. The D isomers of these products, formed by the (*R*)-(+) drug, are not.[92]

In the area of rheumatology, the importance of using optically pure drugs is well illustrated by penicillamine: D-penicillamine has been used for many years in treatment of Wilson's disease and cystinuria and is now widely used in rheumatoid arthritis. It is well established now that this drug, which is chiral, should only be given in the pure D (or *S*) form, because the toxicity of the L (or *R*), or the DL (*RS*) racemic forms, is much greater. This fact was found by trial and error, with some earlier patients on DL-penicillamine experiencing severe adverse side reactions such as optic neuritis. Now only the pure D form is available for prescription (see also 62.2.3.4).[61]

Even more subtle effects arise for drug interactions of a non-chiral drug with a chiral one. Phenylbutazone is not chiral in itself but it can interact with a chiral drug, warfarin, to change the activity of the latter. Phenylbutazone inhibits the oxidative metabolism of the (*S*)-(−) form of warfarin, (which is five times more potent than the (*R*)-(+) form) and thereby decreases its clearance. Conversely, phenylbutazone induces the enzymatic reduction of the (*R*) form thus increasing the clearance.[93] Analysis of total warfarin may indicate little departure from normal pharmacokinetics, but the distribution of eutomer and distomer will have changed markedly.

Another important example of the importance of chirality, related to rheumatology, is that shown by some members of the NSAID family of aryl acids. Certain molecules which inhibit prostaglandin synthetase *in vitro* show *in vivo* antiinflammatory actions. Such compounds include several families of acidic NSAIDs, particularly the aryl acids: salicylates, indomethacin analogs, phenylacetic acids, fenamic acids and enolic compounds. With respect to the indomethacin analogs, an important characteristic has emerged, namely, the requirement for a sinister absolute configuration (the *S* form, which happens to be +) at the chiral centre. For these drugs the (*S*)-(+) enantiomers show dominant, if not exclusive, activity.[94]

Various arylpropionic acids show similar specificity. For most, if not all, the (*S*) enantiomer is the pharmacologically active one, whereas the (*R*) enantiomer is usually much less active, although the ratio of (*S*)/(*R*) activity varies from drug to drug (and species to species). Only one of these drugs, however, is administered as the separated (*S*) enantiomer (naproxen, Naprosyn™). Normally these drugs are considered safe, and one cannot readily differentiate between the relative activities of the (*S*) and (*R*) forms because the *in vivo* half-life is very short, typically one or two hours. In patients with impaired renal function, where clearance is much slower, however, problems can arise. From *in vivo* studies of ibuprofen, it was established that the (*S*)-(+) isomer was responsible for antiinflammatory activity. *In vivo*, however, the (*R*)-(−) isomer may become active because there is stereoselective inversion from (*R*) to (*S*) (but not from *S* to *R*) *in vivo* with a half-life of about two hours.[95] This inversion apparently proceeds by stereoselective formation of the coenzyme A (CoA) ester of the (*R*)-(−)-arylpropionic acid, followed by epimerization and release of the (*S*)-(+)-enantiomer. This epimerization is observed *in vivo* before the oxidative metabolism.[96] Such inversion from (*R*) to (*S*) *in vivo* is also known for fenoprofen[97] and benoxaprofen, and is expected to occur for most of the drugs of this series.[98]

Thus the (*R*) form cannot correctly be described as inert. Statements such as 'the (*R*) form is inert' and the '(*S*) form is pharmacologically active and is therefore also responsible for adverse side effects' must be examined carefully and tested by experiments which are capable of measuring stereospecific differences. In the monitoring of drug levels and metabolites in body fluids, methods which do not distinguish between the (*R*) and (*S*) forms of chiral drugs and their metabolites are likely to yield pharmacokinetic nonsense.

One further point which should be considered is the importance of dose size. Because of the (*R*) ⟶ (*S*) conversion, the dosage of the (*S*) form administered may be as much as two or three times the anticipated dose. One can visualize an elderly 90 lb lady, with decreased renal function, who is administered a racemic drug. She receives the normal dose calculated for a 150 lb person (because of the way the tablets are made up). Because of decreased renal function and increased retention there is time for all the (*R*) enantiomer to be converted to the (*S*) enantiomer. Effectively, she will receive three times the needed dose of the active drug and the area under the dose–time curve will be much greater. It is hardly surprising that adverse side effects sometimes occur.[99]

In summary, clinicians and pharmacologists need to be aware of the potential problems arising from the administration of drugs as racemates. The known differences in pharmacological activity and metabolism exhibited by optical isomers can be applied advantageously, and even exploited by manufacturers, and moreover it can be assumed that such important distinctions will eventually be shown for drugs which have not yet been so extensively studied.

62.2.6 CONCLUSIONS

While the use and study of platinum and gold complexes in cancer and arthritis have resulted in the development of a large research area of current interest, these drugs should be seen in the perspective of other discoveries which have made an enormous impact on medicine: the development of anesthetics, first nitrous oxide and ether, and then chloroform in 1847; the introduction of phenol as an antiseptic by Lister; the discovery of salicylic acid and its analgesic properties in 1876; the discoveries of insulin in 1922 and ascorbic acid in 1927. The use of anesthetics, antiseptics and antibiotics plus modern public health measures providing safe drinking water, sewage and immunization programs have brought about dramatic increases in life expectancy and survival rates, and have made heart disease, cancer and arthritis the modern epidemics. Moreover, a perception of 'a molecular disease' (a term first used by L. Pauling and H. A. Hano in describing sickle cell anemia), has evolved for atherosclerosis and diabetes, and more recently for cancer and arthritis.

Despite the many contributions that chemists and physicists have made to medicine, there remain unanswered problems. Some of them, of course, cannot be resolved by chemists alone, but require political and legislative action, for example the known hazards of smoking to both smokers and non-smokers. The high incidence of lung cancer is well recognized in the 1980s; perhaps less well-known is the fact that lung cancer deaths are expected to exceed those from breast cancer in women in 1985. Occupational health and safety measures in the work setting require input from several professions, but chemists should have a vested interest because chemists as a profession are at a higher risk to certain cancers than are the general population. Chemical research provides data regarding the safe levels and the measurement of levels of toxic substances, as well as the esoteric area of development of new anticancer drugs.

The science of epidemiology with its emphasis on statistics has opened up many areas for research. It should be realized, however, that mortality rates — health statistics dealing with causes of death — are not useful because there are inaccuracies in about 42% of death certificates. Statistics relating to the incidence of disease are therefore more useful. There is still much to be learned in medical research from autopsies: a startling fact for the layman is that the major diagnosis has turned out to be wrong in up to 40% of people who are autopsied. Chemists and other scientists can play a vital role in the more legal and political aspects of medicine, such as publicizing the necessity for autopsies, as well as in the development of chemical tests which will aid diagnoses and in the development of new complexes useful in therapy.

62.2.7 GLOSSARY

Angina	ischemic chest pain
Antiseborrhoeic	against acne and dandruff
DNA	deoxyribonucleic acid
Diuretic	promoting excretion of urine
Dysphagia	difficulty in swallowing
Erythrocyte	red blood cell
GI	gastrointestinal
Iatrogenic	physician-caused
Hematocrit	volume of erythrocytes
LD_{50}	lethal dose, or amount of compound which results in death of 50% of the animals being tested (in a large population)
Lysis	any tissue or cell breakdown
Pica	eating of mud and clay
Pterygium	disease of the conjunctiva of the eye
RA	rheumatoid arthritis
RNA	ribonucleic acid
SOD	superoxide dismutase
Splenomegaly	enlargement of spleen
TPN	total parenteral nutrition
Thrombocyte	platelet

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63

Application to Extractive Metallurgy

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63.1 INTRODUCTION

The extraction of metals from ores is a complex procedure involving a number of physical and chemical separation and purification steps that are designed to produce a pure metal or metal compound with maximum yield at the lowest cost. A simplified diagram illustrating the major processing steps and their interrelationships is shown in Figure 1. The complexity of such processes can be appreciated if one considers the large number of metals that must be economically recovered from ores of widely differing composition and concentration, such as aluminum from bauxite with an Al_2O_3 content of 50–55%, or gold from an ore in which the gold content in the metallic state is as low as 10^{-3}%.

Extractive metallurgy can be conveniently classified into the following three main activities:

(i) mineral processing or ore-dressing, which involves the separation and concentration of the *minerals* from the unwanted or gangue material by a variety of physical and physicochemical techniques that exploit characteristics such as colour, specific gravity, shape and size, charge, magnetic susceptibility and surface properties;

(ii) hydrometallurgy, which, as the name implies, involves the processing of an ore or concentrate by the dissolution, separation, purification and precipitation of the desired metal by the use of aqueous solutions; and

(iii) pyrometallurgy, which produces metals or intermediate products directly from the ore or concentrate by the use of high-temperature oxidative or reductive processes.

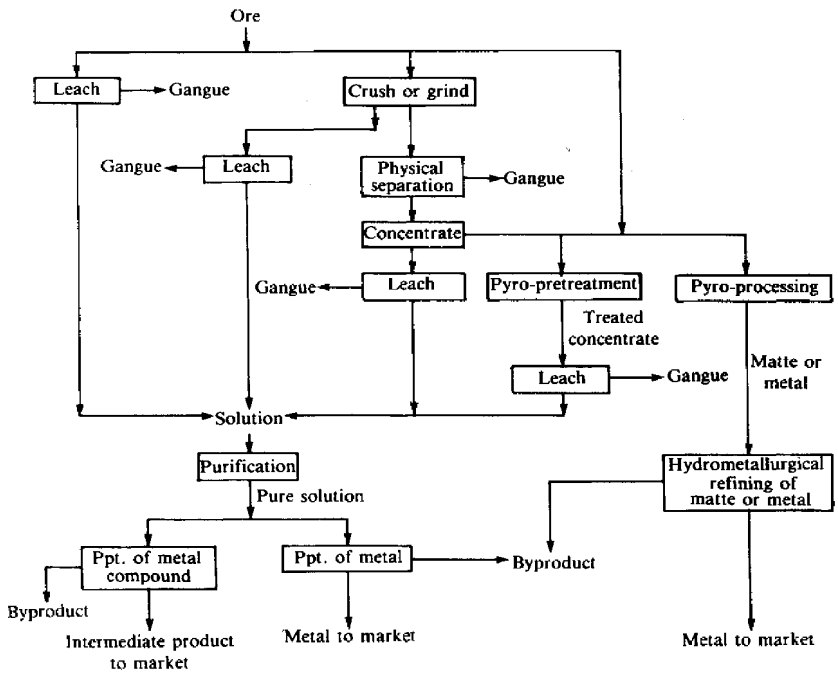


Figure 1 Metallurgical process routes

While it is certainly true that coordination chemistry has its greatest application in hydrometallurgy, several aspects of the ore-dressing and pyrometallurgical operations involve the application of coordination chemical principles, and the indications are that these areas can be expected to develop in the future as our understanding of the chemistry of surfaces and of high-temperature systems develops. For convenience, the following sequence and breakdown will be adopted:

(1) Mineral processing with the emphasis on flotation,
(2) Hydrometallurgy — Leaching
— Separation Processes
— Precipitation, and
(3) Pyrometallurgy with the emphasis on the chemistry of slag systems.

63.2 MINERAL PROCESSING

Materials mined from a mineral deposit usually consist of a heterogeneous mixture of solid phases that are generally crystalline and contain various minerals. Crushing and grinding operations are used to liberate the mineral species from one another and to reduce the size of the solids to a range suitable for subsequent processing. Of the various separation techniques, those of froth flotation and agglomeration exploit the chemical and physical properties of the surfaces of minerals, which can be controlled by various chemical interactions with species in an aqueous phase.

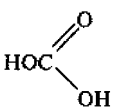
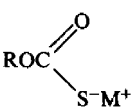
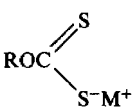
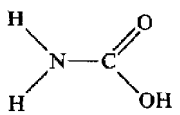
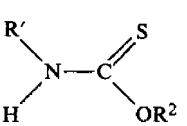
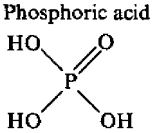
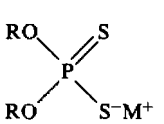
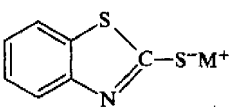
The flotation process is applied on a large scale in the concentration of a wide variety of the ores of copper, lead, zinc, cobalt, nickel, tin, molybdenum, antimony, *etc.*, which can be in the form of oxides, silicates, sulfides, or carbonates. It is also used to concentrate the so-called non-metallic minerals that are required in the chemical industry, such as CaF_2, $BaSO_4$, sulfur, $Ca_3(PO_3)_2$, coal, *etc.* Flotation relies upon the selective conversion of water-wetted (hydrophilic) solids to non-wetted (hydrophobic) ones. This enables the latter to be separated if they are allowed to contact air bubbles in a flotation froth. If the surface of the solids to be floated does not possess the requisite hydrophobic characteristic, it must be made to acquire the required hydrophobicity by the interaction with, and adsorption of, specific chemical compounds known as collectors. In separations from complex mineral mixtures, additions of various modifying agents may be required, such as depressants, which help to keep selected minerals hydrophilic, or activators, which are used to reinforce the action of the collector. Each of these functions will be discussed in relation to the coordination chemistry involved in the interactions between the mineral surface and the chemical compound.

63.2.1 Collectors

Flotation collectors are generally surface active amphipatic molecules, R—X, consisting of a polar group X attached to a non-polar hydrocarbon group R. The interaction of the collector with the mineral surface occurs through the polar group, whereas the non-polar group confers the hydrophobicity to the surface. The polar groups utilized in flotation collectors generally have the ability to coordinate to the metal ion constituting the lattice of the mineral. Typical groups are —OH, $-CO_2H$, —SH, $-OCS_2^-$ (xanthate), $-O_2PS_2^-$ (dithiophosphate), $-NH_2$ and $-SO_3^-$, of which the most widely used are the fatty acids for the flotation of oxides and the thio compounds for the recovery of sulfide minerals.

The most important raw materials for the production of non-ferrous metals, such as copper, lead, zinc, nickel, cobalt, molybdenum, antimony and cadmium, are the sulfide minerals. The use of collectors containing various thio-type functional groups has proved to be the most successful in the flotation of these minerals. Some of these compounds are shown in Table 1.

Table 1 Common Thio Collectors

Parent compound	*Thio derivative*	
Alcohols ROH	RSH	Thiols
Carbonic acid		Alkyl thiocarbonates
		
		Alkyl dithiocarbonates (xanthates)
Carbamic acid		Alkyl thioncarbamates
		
Phosphoric acid		Dialkyl dithiophosphates
		
Xanthate derivatives		Mercaptobenzothiazoles

These collectors are effective only under oxidizing conditions, and it is generally accepted[1,2] that the species that confers hydrophobicity on the mineral surface is either a chemisorbed metal thio compound or the oxidized form of the collector, dithiolate. The amounts of each species formed will depend on the relative stabilities of the metal–sulfur and sulfur–sulfur bonds. The formation of four-membered chelate rings is also possible with soft metal ions such as copper(I) because the largely covalent character of the bond in this instance is able to overcome the strain within the ring by extensive electron delocalization. This could account for the partial selectivity of some of these reagents for the copper minerals,[2] which has been put to good use in the sequential flotation of copper, lead and zinc from complex sulfide ores.[2]

Chelating agents that can form insoluble, hydrophobic chelates on the surface of minerals are potential collectors for the selective flotation of minerals.[3,4] As early as 1927, Vivian[5] reported the use of cupferron, a well-known analytical reagent, as a collector for the flotation of cassiterite (SnO_2). Since then, there have been a number of reports on the use of chelating agents in flotation.

The selectivity potentially offered by these reagents has attracted the attention of many workers who have proceeded on the assumption that these reagents will adsorb onto the surface of minerals with a selectivity for the metal ions of the lattice similar to that found in aqueous solution. Examples of this are dimethyglyoxime for nickel,[6] cupferron for tin,[5] salicylaldoxime for copper and 9-hydroxyquinoline for lead and zinc minerals.[7]

The use of chelating solvent extractants such as the hydroxyoximes for the flotation of oxidized copper ores has been reported;[8,9] unfortunately, although laboratory tests have shown that the use of chelating collectors has potential, they are not yet in widespread commercial use.

A number of attempts have been made to understand the mechanism of the adsorption of chelates on oxide minerals. For instance, IR spectroscopic studies[10] have indicated the presence of a basic monosalicylaldoximate copper complex as well as the bis-salicylaldoximate complex on the surface of malachite (basic copper carbonate) treated with salicylaldoxime. However, other workers[4] have shown that the copper chelate is partitioned between the surface and dispersed within the solution, and that a dissolution–precipitation process is responsible for the formation of the chelate. Research into the chemistry of the interaction of chelating collectors with mineral surfaces is still in its infancy, and it can be expected that future developments will depend on a better understanding of the surface coordination chemistry involved.

63.2.2 Activators

The most widely applied activation procedure is that involving the use of copper(II) ions to enhance the floatability of some sulfide minerals, notably the common zinc sulfide mineral sphalerite.[2] Sphalerite does not react readily with the common thiol collectors, but after being treated with small amounts of copper it floats readily owing to the formation of a surface layer of CuS.[11] A similar procedure is often adopted in the flotation of pyrrhotite (FeS), pyrite (FeS_2), galena (PbS) and stibnite (Sb_2S_3). In the context of coordination chemistry, the major contribution has been to the understanding of the chemistry involved in the deactivation of these minerals, a procedure often adopted in the sequential flotation of several minerals from a complex ore.

A deactivating agent for copper-activated sphalerite is any species that has sufficient affinity for copper(I) or (II) to compete for it with sulfide ions in the surface lattice of the mineral, thus removing it from the surface. Ligands such as cyanide or ethylenediamine, which coordinate strongly to copper, have therefore been found to be the most effective. A knowledge of the stability of the species present in a system composed of H^+, Zn^{2+}, Cu^{2+}, S^{2-} and CN^- ions has enabled[12] the extent of deactivation by cyanide ion to be predicted; the results of these predictions are compared with experimental observations in Figure 2. This approach has been successfully extended to the effects of pH and the presence of other ions such as carbonate on the activation and deactivation processes, and is a pertinent example of the quantitative application of coordination chemistry to complex systems.

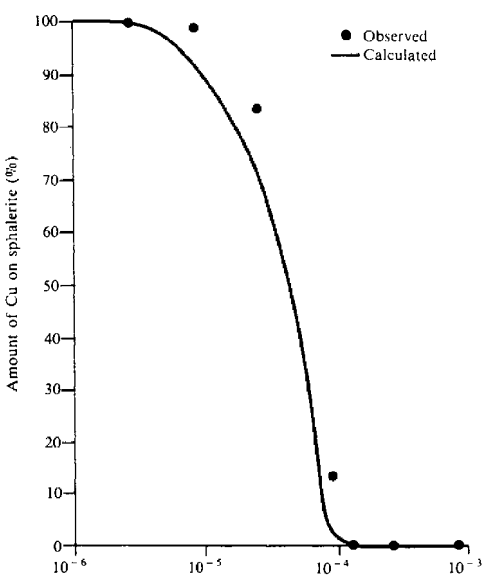


Figure 2 Variation of the extent of deactivation of copper-activated sphalerite as function of the cyanide concentration (after Marsicano *et al.*, ref. 12)

The inadvertent activation of a mineral can often result in an undesirable response to flotation. A typical example is quartz, a highly unreactive mineral whose recovery by flotation is therefore difficult. However, in the presence of metal cations, it can be activated to respond to anionic collectors, as shown by the data[13] in Figure 3. It is of interest that the pH value at which flotation is effective can be related to that at which the monohydroxy complexes of the metal ions are predominantly stable, suggesting a specific adsorption of these species onto the quartz surface. In some cases this can be used for the selective depression of the quartz minerals in, for example, the flotation of pyrite in the presence of cationic collectors such as the long-chain amines.

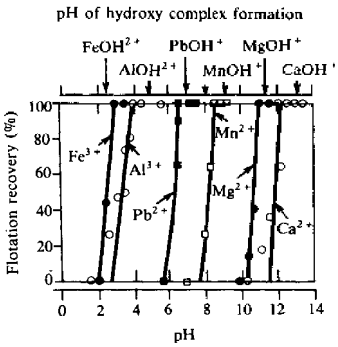


Figure 3 Minimum flotation edges of quartz as a function of pH; 1×10^{-4} M sulfonate, 1×10^{-4} M metal ion (after Fuerstenau and Palmer, ref. 13)

63.2.3 Depressants

The mechanisms of the action of the inorganic depressants are reasonably well understood. The following are examples.

(i) If cyanide is used to suppress the flotation of the sulfide minerals, the greater stability of the cyano complexes over the corresponding thiolates results in the preferential formation of hydrophilic metal cyanide layers for metals such as zinc, copper, iron, nickel, cobalt and even antimony.

(ii) Galena (PbS) is depressed with chromate ions by a mechanism similar to that for cyanide.

(iii) Soluble silicates are used to disperse and to depress the siliceous gangue minerals.

The organic depressants are usually natural products or modified natural products of high molecular mass, and contain numbers of strongly hydrated polar groups that are the basis of their depressant action. Although some of these compounds contain coordinating centres such as hydroxyl, carboxyl and amino groups, the mechanisms whereby these reagents operate is obscure and, as in the case of the chelating collectors, further research into the coordination chemistry of the interaction of these compounds with mineral surfaces is required.

63.3 HYDROMETALLURGY

63.3.1 Leaching Processes

The primary step in a hydrometallurgical process is the dissolution (selectively if possible) of the desired component(s) of the ore, concentrate, or pyrometallurgically produced intermediate. The coordination chemistry of the metal ions produced during leaching is of paramount importance in our understanding of the leaching reactions and in the optimization of the extent of dissolution and of the costs involved. The following list (Table 2) gives an indication of the metals recovered by leaching and of the types of ligands that are employed and those that are potentially useful.

These generally occur in nature as minerals of the oxide or sulfide types, the former including complex oxides such as silicates, carbonates or phosphates. In some cases, such as the precious metals (gold, silver and the platinum group), the elemental form is naturally occurring. While the oxide-type minerals are mostly ionic solids with well-defined stoichiometries and structures, the sulfide minerals exhibit a variety of different structures that are attributable to the essentially covalent character of the bonding in most transition metal sulfides. However, the semimetallic properties of many sulfides show that the degree of covalency varies from a small fraction for zinc sulfide to almost 100% for the copper and iron sulfides.[14] In complex sulfides such as chalcopyrite ($CuFeS_2$), an additional complication is that metal atoms of more than one kind and more than one oxidation state are present. A further characteristic of sulfide minerals is that the composition

Table 2 Metals That Can Be Recovered by Leaching and Types of Ligands Employed

Metal	*Ligand*	*Metal*	*Ligand*
Al	OH^-, Cl^-	Zr, Nb, Mo, Hf, Ta, W	Cl^-, OH^-
Ti	Cl^-	Ru, Rh, Pd, Os, Ir, Pt	Cl^-
Cr	SO_4^{2-}, Cl^-	Ag	NH_3, CN^-, MeCN, Cl^-
Mn	SO_4^{2-}	Au	CN^-, $(NH_2)_2CS$, $S_2O_3^{2-}$, SCN^-, Cl^-
Fe	SO_4^{2-}, Cl^-	Sn	OH^-, Cl^-
Co	SO_4^{2-}, Cl^-, NH_3	Sb	Cl^-
Ni	SO_4^{2-}, Cl^-, NH_3	Pb	OH^-, Cl^-, $MeCO_2^-$
Cu	SO_4^{2-}, Cl^-, NH_3, MeCN	Lanthanides	SO_4^{2-}
Zn, Cd	SO_4^{2-}	U	SO_4^{2-}, CO_3^{2-}
Se, Te	Cl^-		

rarely conforms to the ideal formula, partial substitution of one kind of atom for another (*e.g.* silver for copper or lead) being common.

The chemistry of leaching processes can be broadly classified into two main reaction types: non-oxidative and oxidative (or reductive) processes. In general terms, non-oxidative dissolution occurs when the formal oxidation states of the elements of which the mineral is composed are unchanged during leaching. Examples of such reactions are the leaching of zinc oxides in acid solutions, the dissolution of aluminum oxides in concentrated alkaline solutions, and the dissolution of iron sulfides in acidic solutions to produce hydrogen sulfide. Oxidative (or reductive) dissolution occurs when there is a change in the formal oxidation state of one of the elements during the leaching process. Examples of such reactions include the leaching of uranium dioxide in acidic solutions by the oxidation of uranium(IV) to uranium(VI), of sulfide minerals by the oxidation of sulfur(−II) to the elemental or higher oxidation states, and of gold(0) to gold(I) in alkaline cyanide solutions. It should be clear that the coordination chemistry of both the ions constituting the mineral (or metal) and of the oxidizing (or reducing) agent is a crucial component in the successful dissolution of a mineral and in our understanding of the mechanisms of these reactions.

Attention in the following discussion will be focused on the coordination chemistry of several of these leaching processes as applied in the metallurgical industry and on others that show some potential for future application.

63.3.1.1 Gold and silver

Gold is the most noble of metals (the standard reduction potential for the Au/Au^+ couple is 1.73 V[15]). This property is, of course, the main reason for its durability and for its occurrence in nature usually as the native metal. Despite its generally high resistance to corrosion, gold can be dissolved freely in solutions containing appropriate complexing species. The most stable complexes of gold(I) and gold(III) are those formed with the cyanide ion (β_2 $(Au(CN)_2^-) = 2 \times 10^{38}$ and β_4 $(Au(CN)_4^-) \approx 10^{56}$),[16] and it is therefore not surprising that the majority of industrially important processes involving gold in solution are based on the use of the relatively inexpensive cyanide ligand. In particular, the cyanidation of gold and silver ores has been the most widely employed process for the recovery of these metals for over 100 years.

In the dissolution of gold (or silver) by cyanidation, the milled ore is agitated with dilute alkaline cyanide solution, and the air is introduced (equation 1).

$$4Au + 8CN^- + O_2 + 2H_2O \longrightarrow 4Au(CN)_2^- + 4OH^- \quad (1)$$

This reaction has been shown[17] to occur by a typical electrochemical corrosion mechanism in which the anodic dissolution of the gold, *i.e.*

$$Au + 2CN^- \longrightarrow Au(CN)_2^- + e^- \quad (2)$$

is coupled to the cathodic reduction of oxygen (with peroxide as an intermediate product of reduction). The exceptional stability of the aurocyanide complex is such that dissolution can be achieved even in the presence of considerable amounts of other metals such as copper, zinc and nickel in the ore. The above anodic reaction (equation 2) has been extensively studied[18] and, in terms of its application, the most significant observation is the passivation of the gold surface, as shown by the peak at −0.4 V in the linear-sweep voltammogram, and of a gold electrode in cyanide solution (Figure 4). It is generally agreed that passivation is due to the formation of a strongly adsorbed layer with the stoichiometry AuCN on the surface of the gold. This is consistent with the known[19] linear polymeric structure of gold(I) cyanide in the solid state, in which cyanide acts as a bridging ligand. It is of interest that silver(I), which does not form such a polymeric

structure, does not exhibit passivation, whereas palladium(II), which forms a two-dimensional polymeric structure, exhibits a degree of passivation so severe that it cannot be effectively leached in cyanide solutions. Fortunately, the presence of heavy-metal ions such as those of lead, thallium or mercury in the solution prevents the passivation of gold and, in practice, it is probably seldom encountered as a processing problem. Mechanisms for the action of these ions have been suggested.[18,20]

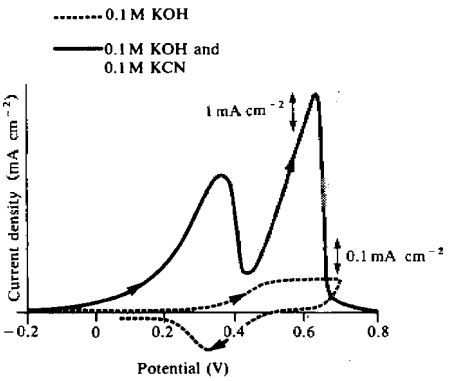


Figure 4 Comparison of the anodic behaviour of a rotating disc gold electrode in 0.1 M KOH with that in a solution of 0.1 M KOH and 0.1 M KCN (after Nicol, ref. 18)

As a result of increasingly stringent environmental regulations, much attention has been devoted in recent years to the possibility that gold and silver can be leached by ligands other than cyanide. Other considerations, for example the presence of excessive quantities of soluble copper in the ore or the occurrence of gold in refractory (to cyanidation) minerals such as arsenopyrite or stibnite, have also prompted the search for alternatives to cyanide. Of the various possibilities, the one most studied[21] and applied is the use of thiourea in acidic solutions with iron(III) as the oxidant. The principal leaching reaction is

$$Au + 2NH_2CSNH_2 + Fe^{3+} \longrightarrow Au(NH_2CSNH_2)_2^+ + Fe^{2+} \quad (3)$$

Extraction is rapid compared to that by cyanidation, and the gold surface is not subject to the passivation observed in alkaline cyanide solutions. At present, the main disadvantage of the process is the high cost of the reagents, which is compounded by the instability of thiourea with respect to hydrolysis and to oxidation under the conditions of the leach.

Other ligands that have been suggested and tested, at least in the laboratory, for the leaching of gold are chloride[22], thiocyanate[23] and polysulfides[25]. Of these, thiocyanate can be expected to play an important role in the future in possible processes for the combined leaching of gold and uranium.

Silver chloride is a common source and intermediate product in many extractive metallurgical processes, for example it occurs in the anode slimes from copper refineries, the residues of leaching processes for base metals, as a product of the chlorination of impure gold–silver bullion, and in photographic waste. A novel process for the leaching and purification of silver chloride, which was devised by Parker *et al.*,[26] is based on the observation that silver chloride is very soluble in some dipolar aprotic solvents containing chloride ion but is much less soluble when water is present. The very different behaviour of the equilibrium

$$AgCl(s) + Cl^- \rightleftharpoons AgCl_2^- \quad (4)$$

in water *versus* dipolar solvents is a function of the slightly stronger solvation of $AgCl_2^-$ and the very much weaker solvation of the chloride ion by the aprotic solvents. These factors can account for an increase of up to 9 log units in the equilibrium constant for the above reaction, therefore dimethyl sulfoxide (DMSO) saturated with calcium chloride (1.4 M) will dissolve almost 200 g of silver per litre. The addition of water to produce a solution with a DMSO content of less than 70% (v/v) results in the precipitation of more than 99% of the silver as a pure product.

63.3.1.2 Copper

The development of hydrometallurgical processes for the extraction of copper from ores and concentrates has been a widespread major research activity for the past 20 years. Coordination chemistry has been applied in many ingenious ways in attempts to devise novel and energy-efficient processes to replace the conventional smelting–electrorefining approach. Several of these processes

have achieved commercial application, while others offer prospects for future development. Ammoniacal leaching processes will be discussed in a later section. Processes based on chloride have received much attention, and several plants currently employ leaching reactions based on the use of chloride.[27] The high stability of copper(I) ion in strong chloride solutions results in a significant change in the chemistry of the copper in such solutions. Copper(II) is therefore a relatively powerful oxidizing agent in concentrated chloride solutions and, in 5 M chloride, is comparable thermodynamically to the iron(III) ion.[28] In addition, the oxidation of copper(I) to copper(II) by oxygen is rapid,[29] and this results in considerably enhanced rates in the oxidative leaching of, for example, sulfide minerals by oxygen in chloride solutions containing copper ions. Furthermore, in the oxidative leaching of copper-containing sulfide minerals, the use of copper(II) as the oxidant in chloride solutions avoids the use of iron(III) with all its attendant problems of iron removal in subsequent processing. The most common copper sulfide mineral is chalcopyrite, and the predominant reaction with copper(II) in chloride solutions is[30]

$$CuFeS_2 + 3Cu^{II} \longrightarrow 4Cu^{I} + Fe^{II} + 2S \qquad (5)$$

As will be discussed later, the recovery of copper from a solution containing copper(I) provides an attractive alternative in terms of energy consumption, and this has led to the search for other ligands that stabilize copper(I). Of these, the nitriles, RCN, provide some interesting and potentially useful processing options, many of which have been explored by Parker and Muir.[31] The nitriles, being rather weak bases, interact much less strongly with a limited number of soft metal ions capable of donating *d*-electrons into an antibonding π-orbital of the nitrile group. Therefore acetonitrile solvates copper(I) and silver more strongly than does water, and this provides the basis for a leaching process for copper metal (impure blister copper produced by smelting, scrap, or from other sources of crude copper).

$$Cu^0 + Cu^{II} \rightleftharpoons 2Cu^{I} \qquad (6)$$

The variation of the equilibrium constant for this reaction in acetonitrile–water mixtures containing dilute sulfuric acid is shown in Figure 5. At pH values below about 5, the curve is more or less independent of acidity because the proton has no significant interaction with acetonitrile in the presence of water. This is an important factor, and distinguishes the nitriles from other ligands such as ammonia and pyridine, which are stronger bases. It should be apparent from the data in Figure 5 that the copper can be effectively leached with copper(II) solutions containing, say, 50% acetonitrile, whereas removal of the acetonitrile by distillation will reverse the equilibrium and result in the precipitation of pure copper powder and regeneration of the copper(II) solution for recycle to the leaching step. This process has undergone extensive pilot-plant evaluation, but has not been implemented on a commercial scale owing to the depressed state of the copper market over the past five to ten years. In theory, copper sulfide and oxide minerals can be leached by the use of a suitably modified version of the above chemistry.

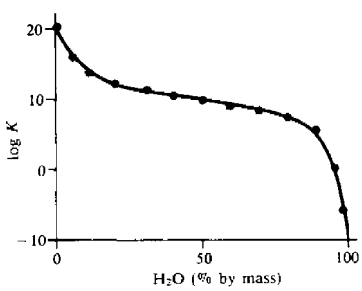


Figure 5 Variation of the equilibrium constant for the reaction $Cu^0 + Cu^{II} \rightleftharpoons 2Cu^{I}$ in mixtures of water and acetonitrile (after Muir and Parker, ref. 31)

63.3.1.3 Nickel and cobalt

Since ammonia forms stable, water-soluble complexes with many metals, leaching can be carried out under alkaline conditions to give these metals in solution. Of particular interest are the metals copper, nickel and cobalt, which form particularly stable amines that have been well characterized as having the following approximate stability constants[16] (at high ionic strength): $Cu^{I}, \beta_2 = 11$; $Cu^{II}, \beta_4 = 13$; $Ni^{II}, \beta_6 = 9$; $Co^{II}, \beta_6 = 5$; $Fe^{II}, \beta_2 < 2$.

It is of particular significance from a processing point of view that iron(II) forms weak complexes and that complexes of iron(III) with ammonia have not been observed. As a result, iron is rejected

from the process as the oxide at the leaching stage, which gives this process a considerable advantage over other acid-based processes for these metals.

This chemistry forms the basis for the successful Sheritt–Gordon ammoniacal leaching process,[32] which is widely applied to the processing of nickel–cobalt–copper sulfide concentrates. A finely ground concentrate of sulfide minerals is leached in ammonia solution in the presence of oxygen to produce a solution containing the amines of copper, nickel and cobalt. As in the leaching of sulfide minerals in chloride solutions, the relatively high stability of copper(I) and its rapid oxidation to copper(II) by oxygen results in considerable catalysis of the leaching process by copper ions. Purification of the leach liquor and its reduction to the metallic state will be reviewed in a later section.

63.3.1.4 Lead

The non-oxidative dissolution of galena (PbS) in acidic solutions is an attractive first step in a hydrometallurgical process for the production of lead metal. The formation of relatively stable chloro complexes with lead ions ($\beta_3 = 2$) results in a displacement of the equilibrium of the reaction

$$PbS + 2H^+ + iCl^- \rightleftharpoons PbCl_i^{(2-i)+} + H_2S \qquad (7)$$

to the right, so that, at elevated temperatures, concentrations of lead of up to 100 g dm^{-3} can be achieved. A knowledge of the formation constants of the various lead chloro complexes has enabled the kinetics of reaction (7) to be predicted[33] on the basis of a kinetic model in which it is assumed that reaction (7) is at equilibrium at the sulfide surface and that the rate-determining step is the diffusion of the various products away from the surface. The results of the calculated and observed rates of dissolution are shown in Figure 6, and the relatively good agreement is further evidence for the invaluable role of coordination chemistry in the quantitative description of applied metallurgical processes.

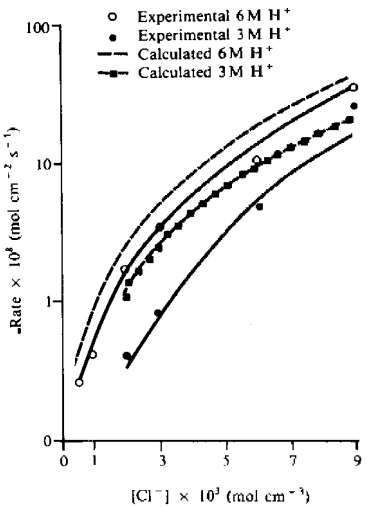


Figure 6 Experimental and calculated rates of dissolution of galena as a function of the chloride concentration at 298 K (after Scott and Nicol, ref. 33)

63.3.1.5 Aluminum

The dissolution of hydrated alumina in concentrated aqueous solutions of sodium hydroxide at elevated temperatures and pressures is the basic step in the extraction of aluminum from bauxite *via* the Bayer process.[34] This dissolution reaction is described by the equation

$$Al_2O_3 \cdot xH_2O + 2NaOH \longrightarrow 2NaAl(OH)_4$$

The high stability of the aluminate ion allows the production of concentrated solutions of aluminum with the virtual exclusion of the main metallic impurity, *viz.* iron as an oxide residue. The resultant impure aluminate solution is clarified and its temperature reduced when the reverse of the above reaction occurs with the formation of $Al_2O_3 \cdot 3H_2O$ by a slow crystallization procedure. The high-purity alumina trihydrate product is calcined and then reduced electrochemically in a molten fluoride bath by the well-known Hall–Heroult process. The major problems in the Bayer process have their origin in the coordination chemistry of aluminum in alkaline solutions. The

most generally accepted structures are $Al(OH)_4^-$ and $Al(OH)_4(H_2O)_2^-$, since the aluminate ion is monomeric, monovalent and has a coordination number of either 4 or 6. Extensive hydrogen bonding between the aluminate ion and the solvent is responsible for the high viscosity of these solutions, which creates major problems in materials handling and heat exchange. In addition, the well-known kinetic inertness of aluminum(III) results in slow rates of crystallization (more than 50 h), requiring large vessels and large volumes of circulating solution and seed material.

63.3.1.6 Uranium

As the most common uranium-bearing minerals such as uraninite (UO_2) are insoluble or dissolve extremely slowly in non-oxidizing aqueous solutions, industrial processes for the leaching of these minerals depend on a reaction that involves oxidation of the uranium from the tetravalent to the hexavalent state with the formation of soluble uranyl species.[35] Depending on the nature of the other constituents of the ore, dissolution is accomplished in acidic sulfate solutions with iron(III) or chlorate ions as the oxidant or in alkaline carbonate solutions with oxygen or peroxide as the most commonly employed oxidants. It is currently generally accepted[35] that the mechanism of the dissolution reaction is electrochemical in nature, anodic oxidation of the semiconducting mineral being coupled to cathodic reduction of the oxidant on the mineral surface.

The rate of leaching of UO_2 by iron(III) is significantly higher in sulfate than in perchlorate solutions[35] and, at a pH value of 1, it passes through a maximum as the sulfate concentration is increased, as shown in Figure 7. Also shown is the effect of the sulfate concentration on the cathodic reduction of iron(III) at a UO_2 surface. The close similarity of the two curves demonstrates that the influence of the sulfate ion on the leaching rate is a cathodic phenomenon. Furthermore, the maximum, at a sulfate:iron(III) ratio of approximately 1:1 suggests that the species $FeSO_4^+(aq)$ is the most electroactive of the various iron(III)–sulfato complexes under these conditions.

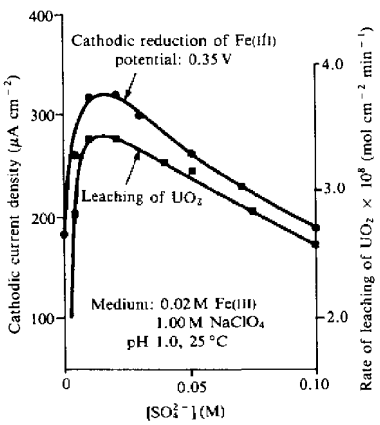


Figure 7 Influence of sulfate on cathodic reduction of Fe^{III} and leaching of UO_2 by Fe^{III} (after Nicol, Needes and Finkelstein, ref. 35)

Complex uranium ores are often associated with phosphate-bearing minerals, and the presence of soluble phosphate has been found to adversely affect the recovery of the uranium. Studies such as those outlined above have established that, although the iron(III)–phosphonato complexes are more reactive, the decreased leaching rate in the presence of phosphate is due to the formation of insoluble, non-conducting layers of uranyl phosphate on the surface of the mineral.

The uranyl ion forms unusually strong soluble complexes with the carbonate anion[16] ($\beta_3 > 20$), and this has formed the basis for the use of alkaline carbonate solutions in the leaching of uranium, particularly where the ore is leached directly from the ore body (leaching *in situ*). The rate of dissolution increases with increasing concentration of carbonate but reaches a limiting value at concentrations above about 1 M. It has been shown[36] that this is due to the rate-determining formation of a layer of hydrated UO_3 on the surface, which subsequently dissolves by forming complexes with the carbonate ions.

63.3.2 Solvent-extraction Processes

Solvent extraction is a well-established method of separation in the field of extractive metallurgy. First applied to the extraction of uranium for nuclear purposes in the early 1940s, the technique currently now finds widespread use in the recovery of uranium, copper, zinc, cobalt, nickel,

vanadium, tungsten and molybdenum, as well as in separations amongst gold and the platinum-group metals, in separation amongst yttrium and the rare-earth metals, in the separation of niobium and tantalum, and in the separation of zirconium and hafnium. Although the origin of many of the commercial processes is undoubtedly empirical, subsequent studies of a fundamental nature have often enabled the underlying chemical principles to be clearly identified.

Solvent-extraction systems can be classified conveniently according to the nature of the reaction involved in the extraction process, of which the following types can be identified.

(a) Extraction by physical distribution involves a simple molecular distribution of the solute between the aqueous phase and an inert solvent (*i.e.* one containing no atoms with electron-donor properties). Such a situation arises only for solutes that are scarcely solvated in the aqueous phase. Few, if any, such systems are found in the field of extractive metallurgy, but they are typified by, for example, the extraction of ruthenium tetroxide into a solvent such as carbon tetrachloride.

(b) Extraction by solvation involves the replacement by the extractant of some or all of the coordinated water molecules from a metal cation (or hydrogen ion) to form a species that is soluble in the organic phase. A typical example is the extraction of uranyl nitrate by tri-*n*-butyl phosphate (TBP)

$$UO_2(H_2O)_6^{2+} + \overline{2TBP} + 2NO_3^- \longrightarrow \overline{UO_2(NO_3)_2(TBP)_2} + 6H_2O \qquad (8)$$

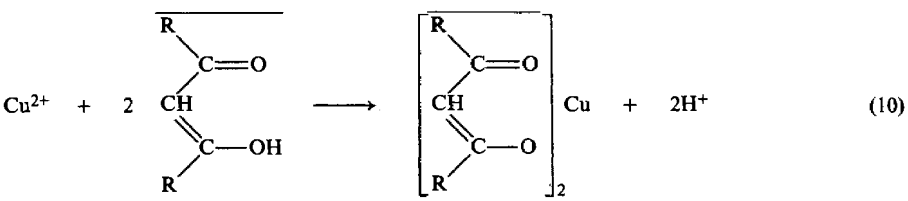
where the bars denote the presence of the species in the organic phase. Solvating extractants are most characteristically oxygen-containing organic molecules such as ethers, ketones and neutral organophosphorus compounds.

(c) Extraction by anion exchange is characterized by the extraction of an anionic metal species in the form of an ion pair with a suitable cation, following the exchange with a simple (non-metallic) anion between the organic and aqueous phases. A typical example is the extraction of cobalt(II) from chloride solutions by an organic solution of an amine salt:

$$[CoCl_4^{2-}] + 2R_3NH^+Cl^- \longrightarrow (R_3NH^+)_2[CoCl_4^{2-}] + 2Cl^- \qquad (9)$$

Often, the cationic component of the ion pair is formed by the protonation of a compound of appreciable basicity, most typically a nitrogen-containing base. Alternatively, the cation may be of the quaternary ammonium, phosphonium or arsonium type.

(d) Extraction by cation exchange involves the formation, by the extracted metal cation, of an electrically neutral coordination complex with the extractant by displacing another cation (most commonly a hydrogen ion). Frequently, the formation of the extractable complex involves chelation as, for example, in the extraction of copper(II) by the enol form of a β-diketone:



(10)

When the cation displaced from the extractant is a hydrogen ion, as in reaction (10), the extractability of the metal shows a distinct dependence on the pH value of the aqueous phase. Such systems are conveniently characterized by the pH value at which the concentrations of metal in the organic and aqueous phases are equal at a stated concentration of extractant, this being denoted the $pH_{0.5}$ value for the given metal.

In the following sections, the most important commercial applications of solvent-extraction technology in the field of extractive metallurgy are discussed in terms of the coordination chemistry relevant to the extraction process. The sole criterion for the inclusion of a given process is that it should have been utilized on an industrial scale. It may be noted that several interesting extraction systems in the early stages of development have been excluded on this basis, despite the pertinence of the chemical principles involved.

63.3.2.1 Solvent extraction of base metals by carboxylic acids

Carboxylic acids represent a group of readily available and relatively inexpensive extractants. They have found rather limited application in commercial processes, however, probably on account of their generally low selectivity and poor pH functionality. Nevertheless, they have been used for the separation of copper from nickel,[37] the removal of iron from the rare-earth metals,[38] separations among yttrium and the rare earths,[39] the recovery of indium[40] and gallium,[41] the removal of

impurities from cobalt electrolytes,[42,43] and the coextraction of cobalt and nickel before further processing.[44]

The extraction of some metal ions by Versatic 10 acid (a commercial product consisting mainly of 2-ethyl-2-methylheptanoic acid and similar highly branched isomers) is shown in Figure 8. The order of extraction of the metals investigated in a recent study[45] is $Tl^{III} > Pd^{II} > Hg^{II} \approx Fe^{III} > In^{III} > Th^{IV} > UO_2^{II} \approx Al^{III} > Cu^{II} > Pb^{II} > Yb^{III} > Ag^{I} > Zn^{II} > Nd^{III} > Ce^{III} > La^{III} > Cd^{III} > Ni^{II} > Co^{II} > Fe^{II} \approx Mn^{II} > Ca^{II} > Sr^{II} > Mg^{II} \approx Ba^{II}$. This series can be largely rationalized on the basis of the magnitude of the stability constants for complexation of the respective metal ions by a typical carboxylate anion such as acetate.[45] Earlier comparisons between such selectivity series and the order of precipitation of the metal hydroxides[46,47] have a fundamental basis only insofar as RCO_2^- and OH^- both belong to the class of ligands that are anions of a weak acid.[48] Clearly, such a comparison cannot account for discrepancies such as the relative positions of calcium, strontium and magnesium. In contrast, the poor extraction of magnesium can be understood readily in terms of the expected stability constants for formation of the carboxylate complexes, such a displacement of magnesium from the usual order (*e.g.* K_1 for the formation of the acetate complexes Mg > Ca > Sr > Ba) commonly occurring with ligands of increased steric complexity, as a result of the small size of the Mg^{2+} ion (0.64 Å, as compared with 0.99 Å for Ca^{2+} and 1.13 Å for Sr^{2+}).[48]

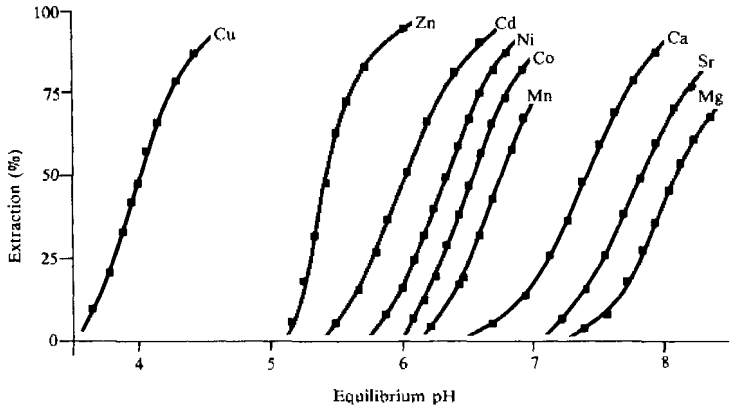


Figure 8 Extraction of some divalent metals (0.05 M as nitrates) from 1.0 M sodium nitrate solutions by 0.50 M solutions of Versatic 10 acid in xylene at 20 °C

For the divalent metals of the first transition series, the order of extraction follows that expected on the basis of the Irving–Williams series[49] for the stability constants of the octahedral complexes, *viz.* Mn < Fe < Co < Ni < Cu > Zn. However, although copper(II) can be readily separated from the remaining metals, mutual separations in the group nickel, cobalt, iron and manganese are not readily accomplished. For example, the difference between the $pH_{0.5}$ values for the extraction of nickel and cobalt was found to lie between 0.0 and 0.2 pH units for a range of different aliphatic and aromatic carboxylic acids.[50] The removal of nickel from cobalt-containing solutions by extraction with carboxylic acids therefore requires a process consisting of many separate stages if a high efficiency is to be achieved, and is believed to have been applied on a commercial basis only in the Soviet Union.[42,43]

Although it is evident from electronic spectra that nickel(II) and cobalt(II) form complexes of octahedral symmetry with carboxylic acids,[50] the exact stoichiometry of the extracted complexes has not been fully established. However, it is apparent that, in addition to the coordination of the two carboxylate anions (A^-) required to give an electrically neutral complex, further coordination of undissociated carboxylic acid ligands (HA) occurs so that the metal ion can achieve its preferred octahedral coordination, complexes of the type $NiA_2(HA)_4$ and $CoA_2(HA)_4$ being formed.[51,52] Oligomerization of the complexes presents an alternative means for the achievement of an octahedral coordination, and the presence, in organic extracts, of dimeric compounds of the type $Ni_2A_4(HA)_4$ and $Co_2A_4(HA)_4$ has been suggested on the basis of metal distribution data. However, no consideration appears to have been given to the structure of such complexes.[51–53]

The Sumitomo Metal Mining Co. in Japan uses a carboxylic acid extractant to recover nickel and cobalt from a solution obtained from the pressure leaching of metal sulfide concentrates with sulfuric acid.[44] Iron, copper, zinc and manganese are removed from the leach liquor by conventional precipitation methods prior to the extraction of nickel and cobalt into a 40–60% solution

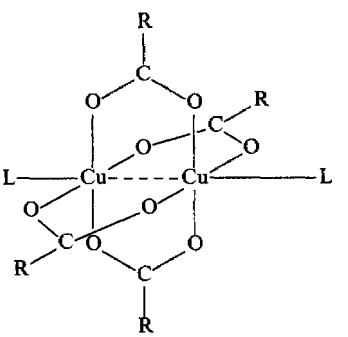
of Versatic acid in kerosene. Ammonia solution is used to adjust the equilibrium pH value to 6.9:

$$(Ni,Co)SO_4 + \overline{nH_2A_2} + 2NH_3 \longrightarrow \overline{(Ni,Co)A_2(HA)_{2n-2}} + (NH_4)_2SO_4 \quad (11)$$

The ammonium sulfate contained in the raffinate is treated with lime to produce ammonia for recycle, and the extracted nickel and cobalt are transferred to a chloride medium (for subsequent separation by amine extractants, as described in Section 63.3.2.4) by stripping with 25% hydrochloric acid solution:

$$\overline{(Ni,Co)A_2(HA)_{2n-2}} + 2HCl \longrightarrow (Ni,Co)Cl_2 + \overline{nH_2A_2} \quad (12)$$

The high affinity shown by carboxylic acids for copper (II) compared with the remaining divalent metals of the first transition series appears to be due in part to the stabilization of the extracted complexes by the formation of the well-known dimeric structure (**1**) in which copper(II) carboxylates exist in the solid state and in non-donor solvents.[54] The axial ligands, L, consist of undissociated carboxylic acid molecules[55] or, in the absence of an excess amount of extractant, they may consist of water or other solvent molecules.[56] Copper was successfully removed from nickel sulfate solutions on the base-metal plant at Matthey Rustenburg Refiners in South Africa by being extracted into Versatic 10 acid at a controlled pH value. The process is believed to have been discontinued only because improvements in the selective leaching of copper and nickel rendered it unnecessary.



(**1**)

The use of carboxylic acids for the removal of iron(III) from solutions of the rare-earth metals has been reported,[38] but has not been described in detail. The stoichiometries of the extracted complexes of iron(III) have not been clearly established. The *n*-decanoic acid complex has been variously described as $(FeA_3)_3$ and $Fe_3A_{9-x}(OH)_x(HA)_x$[51] or $[Fe(OH)A_2]_2$ and $[Fe(OH)_2A{\cdot}HA]_2$,[57] the *n*-octanoic acid complex as $(FeA_3{\cdot}H_2O)_3$,[58] the naphthenic acid complex as FeA_3,[47] and that of Versatic 10 acid as $[FeA_3(HA)_x]_y$ or $[Fe(OH)A_2]_3$.[59]

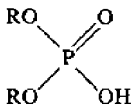
Versatic acid has also been used by Thorium Ltd. in England for the production of pure europium(III), lanthanum(III) and yttrium(III) oxides.[39] The extracted carboxylate complexes of the lanthanides(III) have been shown[60] to have the composition $MA_3(HA)_3{\cdot}xH_2O$, where $x = 1$ or 2. Extraction of the lanthanides(III) by Versatic acid has been reported to increase progressively with atomic number[39] whereas, for C_9 carboxylic acids of similar structure, the extraction was shown to increase from lanthanum to samarium, and then to decrease from samarium to lutetium.[60] A similar pattern, in which extraction increases from lanthanum to europium and decreases from gadolinium to ytterbium, was found for acids of the naphthenic type[61] (alkylcyclopentanecarboxylic acids derived from the refining of petroleum). It is of interest that a plot of the stability constants (K_1) for the formation of the acetate complexes of the lanthanides also reveals a maximum at samarium.[62] This effect can probably be attributed to opposing contributions from the enthalpy and entropy terms to the free-energy change on complex formation.

Versatic acid has been used in Japan to recover indium and gallium from solutions obtained from the leaching of bauxites, zinc minerals, coal ash and flue dusts.[40,41,63] Extraction is carried out at a pH value of 2.5 to 4.0; some coextraction of tin(II), iron(III) and aluminum(III) occurs if these metals are present. In the extraction of indium(III) by *n*-hexanoic acid,[64] the predominant species in the organic phase was found to be $InA_3(HA)_3$ whereas in the extraction by *n*-decanoic acid[65] the existence of trimeric $(InA_3{\cdot}HA)_3$ and hexameric $[InA_2(OH)]_6$ species was also postulated.

The literature pertaining to the structures of extracted metal carboxylate complexes has been reviewed.[66]

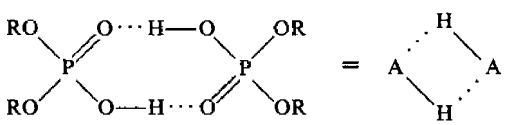
63.3.2.2 *Solvent extraction of base metals by organophosphorus acids*

The use of organophosphorus acids, such as di(2-ethylhexyl)phosphoric acid (D2EHPA; di(2-ethylhexyl) monohydrogen phosphate; **2**; R = $C_4H_9CH(Et)CH_2$), is now well established in the recovery of base metals. This reagent has found commercial application in the separation of cobalt from nickel,[67,68] the separation of zinc from impurities such as copper and cadmium,[69] the recovery of uranium,[68] beryllium[70] and vanadium,[71] and in separations involving yttrium and the rare-earth metals.[72,73]

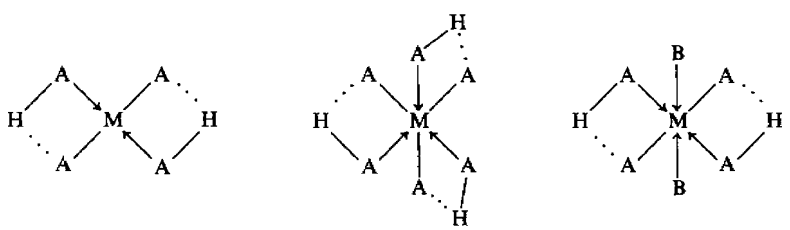


(2)

It is a well-known and important feature of the chemistry of organophosphorus acids that they exist in the form of dimeric molecules when dissolved in organic solvents of low polarity, such as the aliphatic and aromatic hydrocarbons that are typically used as diluents in commercial extraction processes.[74] The formation of these dimers represents a self-solvation of the monomeric reagent *via* the formation of intermolecular hydrogen bonds, a stable eight-membered ring (**3**) being formed, which can conveniently be represented in the abbreviated form (**4**). Moreover, it is apparent that, when a sufficient amount of excess extractant is available, these cyclic structures also persist in the extracted metal complexes, only one proton being displaced from each dimer, which then acts as a bidentate ligand.[75] For divalent metal ions that show a preference for tetrahedral coordination and trivalent metals that prefer octahedral symmetry, coordination-saturated complexes such as (**5**) and (**6**) are formed respectively. However, for those divalent metals that show a preference for octahedral coordination, it is clear that additional ligands (**B**) must be bound to the metal ion so that the preferred coordination number can be achieved. Complexes such as (**7**) are then formed. If a sufficient amount of excess organophosphorus acid is available, these additional ligands consist of undissociated molecules of the extractant (B = HA or H_2A_2 in structure **7**). In the absence of an excess amount of extractant, water or other solvent molecules occupy the remaining sites in the octahedral complexes.

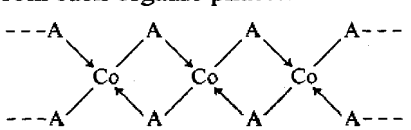


(3) (4)



(5) (6) (7)

When large amounts of metal ions are loaded into organic phases containing organophosphorus acids, the limiting ratio of metal to extractant of 1:2 is approached, and polymerized complexes such as (**8**) are then formed, in which the PO_2^- group acts as a bridging ligand between adjacent metal ions.[76] Solid products of composition such as CoA_2 and $NiA_2(H_2O)_2$ have been obtained by the removal of the solvent from such organic phases.[77]



(8)

The extraction of some metal ions by di(2-ethylhexyl)phosphoric acid is shown in Figure 9.[7] The order of extraction of the divalent metals of the first transition series, *viz.* Zn > Cr > M > Cu > Fe > Co > Ni > V, shows important differences from that observed with carboxyli acid extractants, particularly with respect to the relative positions of zinc and copper and of coba

and nickel. The above order clearly shows no correlation with the Irving–Williams series for the stability constants of octahedral complexes, but appears instead to reflect the ease with which the respective metal ions adopt the tetrahedral configuration (or, for copper(II) and chromium(II), a tetragonally distorted octahedral configuration) that is favoured by the bulky dimeric ligands. Therefore, an important contribution to the selectivity series is made by the magnitude of the differences in the ligand-field stabilization energies of the octahedral and tetrahedral complexes of the respective metals, which lie in the order Zn, Mn < Fe < Co < Cu, Cr < Ni, V. Evidence from spectral, thermogravimetric, magnetic and ESR studies,[77,79,80] as well as from a study of the effect of temperature upon metal distribution,[81] suggests that the zinc(II) and manganese(II) complexes have tetrahedral structures, whereas the copper(II) complex has a square-planar or distorted octahedral structure. The nickel complex has the octahedral structure (7), the axial ligands B consisting of undissociated extractant molecules (HA or H_2A_2) or water molecules, depending upon the extraction conditions. The complex has been variously formulated as $Ni(HA_2)_2(HA)_2$,[82,83] as $Ni(HA_2)_2(H_2A_2)_2$[84] and, more generally, as $Ni(HA_2)_2(H_2A_2)_x(H_2O)_{2-x}$.[85] For cobalt(II), tetrahedral (blue) and octahedral (pink) forms of the complex exist in equilibrium,[81,86] the tetrahedral form being increasingly favoured as the temperature is raised, owing to the entropy contribution of reactions such as

$$\overline{Co(HA_2)_2(H_2O)_2} \longrightarrow \overline{Co(HA_2)_2} + 2H_2O \qquad (13)$$

This effect has been utilized to enhance the separation of cobalt from nickel, since commercial extraction processes usually operate at temperatures of 50 to 70 °C. Thus, the difference between the $pH_{0.5}$ values for the extraction of cobalt and nickel from 1.0 M ammonium nitrate solutions by 0.50 M D2EHPA in xylene increases from 0.16 pH units at 0 °C to 0.43 pH units at 20 °C and 0.78 pH units at 50 °C.[85] At low metal loadings, the tetrahedral cobalt(II) complex has been unequivocally formulated as $Co(HA_2)_2$,[82,83,85] whereas, at high metal loadings, a polymeric species is formed with a composition approaching the limiting stoichiometry of CoA_2.[76] The structure of the pink octahedral complex is undoubtedly analogous to that of the corresponding nickel(II) complex.

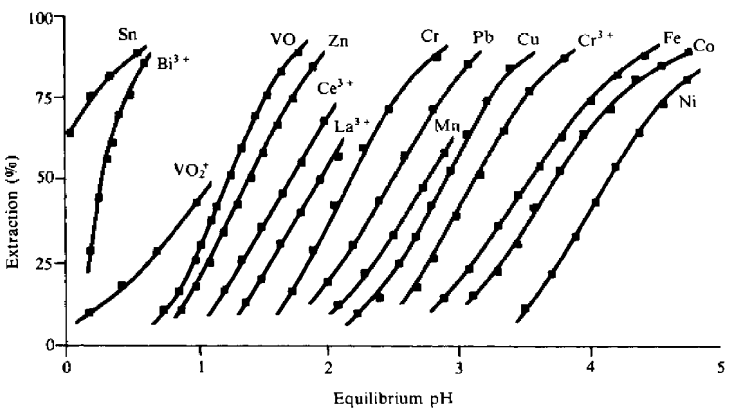
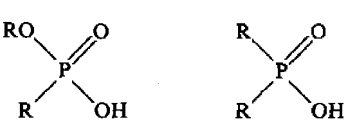


Figure 9 Extraction of some metal ions (divalent unless shown otherwise) by 0.50 M solutions of di(2-ethylhexyl)phosphoric acid in xylene at 20 °C

Recently new reagents were introduced that extract cobalt entirely in the tetrahedral form,[85,87,88] thus enhancing the separation of cobalt and nickel, since the complexes of the latter metal retain an octahedral structure. In these reagents of the phosphonic and phosphinic acid types (structures **9** and **10** respectively), the closer proximity of one or both of the alkyl groups to the metal-coordinating site brings about considerable destabilization of the octahedral nickel complex relative to the tetrahedral cobalt complex, owing to steric crowding, particularly if the alkyl group is branched at the α-carbon atom. So, for example, when R = 2-ethylhexyl, the separation between the curves for cobalt and nickel extraction for a 0.2 M solution of extractant in toluene at 20 °C increases from 0.53 pH units for the phosphoric acid to 1.42 for the phosphonic, and 1.93 pH units for the phosphinic acid.



(9) **(10)**

The Nippon Mining Co. refinery in Japan, which had previously used D2EHPA to extract cobalt from solutions obtained in the leaching of a mixed cobalt–nickel sulfide in sulfuric acid, changed in 1978 to the new extractant 2-ethylhexyl 2-ethylhexylphosphonate enabling a much-improved selectivity for cobalt over nickel to be obtained.[89,90] The process is carried out in three countercurrent stages with an organic solution of phosphonic acid that has been converted to the ammonium salt by contact with aqueous ammonia:

$$\overline{H_2A_2} + NH_4OH \longrightarrow \overline{NH_4HA_2} + H_2O \tag{14}$$

$$\overline{2NH_4HA_2} + Co^{2+} \longrightarrow \overline{Co(HA_2)_2} + 2NH_4^+ \tag{15}$$

Any nickel that is coextracted with the cobalt is displaced from the organic phase by contact with a concentrated solution of cobalt(II) sulfate:

$$\overline{Ni(HA_2)_2(H_2A_2)_n} + Co^{2+} \longrightarrow \overline{Co(HA_2)_2} + \overline{nH_2A_2} + Ni^{2+} \tag{16}$$

Cobalt is stripped from the organic phase with the spent electrolyte from the cobalt electrowinning circuit

$$\overline{Co(HA_2)_2} + H_2SO_4 \longrightarrow \overline{2H_2A_2} + CoSO_4 \tag{17}$$

and the neutral solution of cobalt(II) sulfate so formed provides the feed to electrowinning.

The high affinity of organophosphorus acid extractants for zinc(II) has been utilized in several commercial processes. The Nippon Mining Co. uses D2EHPA to extract zinc selectively from cobalt and nickel prior to separation of the latter metals, using the phosphonic acid extractant described above. Zinc is extracted in a single contact at an equilibrium pH value of 2 to 3, where negligible coextraction of cobalt and nickel occurs (Figure 9). Zinc is also recovered with D2EHPA at plants in Spain[69] and Portugal[91] after a preliminary extraction from chloride solutions with an amine salt (Section 63.3.2.4). The zinc(II) chloride strip liquor obtained from the first extraction cycle is extracted with a solution of D2EHPA, milk of lime being used to adjust pH:

$$ZnCl_2 + \overline{2H_2A_2} + Ca(OH)_2 \longrightarrow \overline{Zn(HA_2)_2} + CaCl_2 + 2H_2O \tag{18}$$

The extracted zinc is transferred to a sulfate medium, which is preferred for the electrowinning of zinc, by stripping with a solution containing sulfuric acid (being spent electrolyte from the electrowinning plant):

$$\overline{Zn(HA_2)_2} + H_2SO_4 \longrightarrow ZnSO_4 + \overline{2H_2A_2} \tag{19}$$

The concentrated solution of zinc(II) sulfate produced in this way forms the feed to the zinc electrowinning stage, and the regenerated D2EHPA is recycled to extraction.

Zinc(II) is extracted selectively over copper(II) and cadmium(II), but some iron(III) is coextracted into the organic phase. (Iron(III) is, in fact, more strongly extracted than zinc(II) under equilibrium conditions, but the rate of extraction of the former metal is slow.) Any iron(III) that is extracted remains in the organic phase during the stripping of the zinc and is removed subsequently in a separate step with a strong solution of hydrochloric acid.

Organophosphorus acid extractants have also been used in the commercial recovery and separation of the rare-earth metals. The largest operation of this type is located at the Mountain Pass mine in California, which is owned by the Molybdenum Corporation of America and is the world's principal source of rare-earth compounds. The plant was inaugurated in 1965 to produce europium(III) oxide of greater than 99.9% purity for use in the manufacture of red phosphors for colour television.[92] Subsequently, facilities were installed for the production of samarium(III) oxide for use in the manufacture of samarium–cobalt magnets for high-efficiency electric motors, and of gadolinium(III) oxide for use in the image enhancement of X-ray films and in the control of nuclear reactors.[93] Other technical-grade rare-earth products are also produced.

In the various solvent-extraction circuits employed in this process, use is made of a solution of D2EHPA in kerosene as the extractant. The selective recovery of the various metals is achieved by careful control of the equilibrium pH value of the aqueous phases in the multistage extraction and stripping operations. After the leach liquor has passed through two separate circuits, each of which comprises five stages of extraction and four of stripping, the europium product is obtained initially as a solution of europium(III) chloride. Further purification of the product is accomplished by reduction with amalgamated zinc to Eu^{2+}, which is by far the most stable of the divalent lanthanide ions with respect to the reduction of water (*cf.* the redox potentials of the Eu^{3+}/Eu^{2+} and Sm^{3+}/Sm^{2+} couples, which are −0.43 and −1.55 V respectively[94]). Sulfuric acid is added to the

europium(II) solution to precipitate the insoluble sulfate, which is subsequently calcined to europium(III) oxide of high purity.

Other commercial operations known to have used organophosphorus acids for the recovery of rare earths are those of Thorium Ltd. in England,[39] the Megon Company in Norway,[73,95] and Denison Mines in Canada.[96,97]

The extracted complexes have been shown [98–100] to have the composition $M(HA_2)_3$. Although the lanthanides commonly form complexes in which the metal ion is eight- or nine-coordinate, octahedral coordination appears to be favoured by the complexes with organophosphorus acids, presumably because of the steric demands of the bulky dimeric ligands. Under conditions of high metal loading, the extracted complexes form insoluble gels, which are polymeric compounds of stoichiometry $(MA_3)_n$, where n is approximately 600 for lanthanum and ytterbium, and approximately 4000 for yttrium and holmium.[101] The extractability of the rare-earth metals by D2EHPA increases monotonically with increasing atomic number,[98] a plot of log D (where D is the distribution ratio of the metal between the organic and aqueous phases) against atomic number (Z) being approximately linear, with an average separation factor ($\beta = D_{z+1}/D_z$) of about 2.5. Yttrium(III) lies on the same straight line if assigned an artificial atomic number of 67.5, *i.e.* between those of holmium and erbium.

For the trivalent lanthanides[99,100] and actinides,[99] as well as for yttrium and scandium,[75] the equilibrium constant for the extraction reaction has been shown to vary inversely with the ionic radius of the metal ion. It has therefore been concluded that the extracted complexes are all of the $M(HA_2)_3$ type, involving predominantly ionic metal–ligand bonds.[75] The similarity of the IR spectra of the scandium(III) and thorium(IV) complexes of D2EHPA to those of the alkali metals is also indicative of the importance of ionic bonding.[102]

Scandium(III) is extraordinarily strongly extracted by D2EHPA, because its ionic radius is small (Pauling radius 0.81 Å) compared to those of the lanthanides (0.93 to 1.15 Å), and this property has been used in the recovery of scandium as a byproduct of uranium processing. Thus, at the Vitro Chemical Company in Salt Lake City, Utah, scandium was coextracted with uranium into an organic phase containing dodecyl dihydrogen phosphate.[103] The uranium was selectively stripped into 10 M hydrochloric acid, while the scandium remained in the organic phase and was removed subsequently by stripping with hydrofluoric acid to produce a precipitate of scandium(III) fluoride. On a plant installed to recover scandium, thorium, yttrium and the heavy lanthanides from waste sulfate liquor from the Port Pirie uranium refinery in South Australia, the metals were coextracted into 0.1 M D2EHPA in kerosene.[104] All the products except scandium were stripped with 4.5 M sulfuric acid, and the scandium was recovered from the organic phase, which was contacted with a 2.5 M solution of sodium hydroxide to precipitate scandium(III) hydroxide. The precipitate was then separated by filtration.

Thermodynamic measurements on the partition of the lanthanides between 2-ethylhexyl phenylphosphonate in heptane and aqueous nitric acid have shown that changes in entropy are largely responsible for the increased stability of the extracted complexes of the metals from lanthanum to promethium, whereas the decreasing enthalpy of the system is the major factor contributing to the continued increase in the stability of the complexes of the remaining metals.[105] Thus, for the reaction in the interval from lanthanum to promethium, the enthalpy of partition becomes decreasingly exothermic, whereas a very pronounced increase occurs in the entropy change (about 17 entropy units). In contrast, in the interval from promethium to lutetium, the partition process becomes increasingly exothermic, whereas the entropy changes remain approximately constant. Further scrutiny of the thermodynamic data for this system revealed that plots of the change in the free energy of reaction against atomic number show a distinct 'tetrad' effect,[106] as had been observed previously in plots of log D against the atomic number of the lanthanides.[107,108] The effect is also clearly discernible in earlier distribution data for D2EHPA.[109] Peppard[108] has proposed the general hypothesis that, in systems involving all fifteen lanthanides(III), the points on a plot of the atomic number (Z) against the logarithm of a suitable numerical measure of a given property of these elements may be grouped into four tetrads by the use of four smooth curves without inflections, the gadolinium point being common to the second and third tetrads, and the extended smooth curves intersecting additionally in the regions where $Z = 60$ to 61 and 67 to 68. The origin of the effect has been attributed to the quantum mechanical interelectronic repulsion energy of the 4*f*-electrons.[110] In practical terms, the tetrad effect makes the separation of those adjacent pairs of elements that lie on the zone of the shallowest curvature of each tetrad, *viz.* Pr/Nd, Eu/Gd, Dy/Ho and Yb/Lu, even more difficult.[73,111]

Few details have been revealed concerning the commercial extraction of beryllium by organophosphorus acids. However, alternative processes involve the stripping of the loaded organic phase

with mineral acid followed by the precipitation of beryllium(II) hydroxide with alkali, or the direct precipitation of beryllium(II) hydroxide from the loaded organic phase.[70] The selective extraction of beryllium(II) over aluminum(III) presents a major difficulty,[112] although the separation of these metals can be achieved in a multistage process with careful control of the equilibrium pH values.

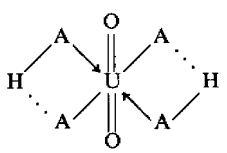
The extracted beryllium(II) complex is of the type $Be(HA_2)_2$, and, as would be expected from the small ionic radius of the cation (0.34 Å), the steric complexity of the organophosphoric acid exerts a marked effect on its extractive power.[113] Although beryllium is extracted more strongly than the other alkaline earth metals, it is extracted less strongly than would be expected on the basis of the linear extrapolation of a plot of the logarithm of the extraction constants against the reciprocal of the ionic radii for barium, strontium, calcium and magnesium.[75] This is also a consequence of the very small ionic radius of beryllium(II), which is less than the limiting value that would result in oxygen–oxygen contact of the ligands, even for tetrahedral coordination.[75]

Organophosphorus acids were among the first extractants to be used in the commercial recovery of uranium from solutions obtained by the leaching of low-grade ores with sulfuric acid. In the so-called Dapex process,[70,114] the leach liquor is extracted with a solution of about 0.1 M D2EHPA in kerosene, and the pH value of the aqueous phase is adjusted to close to 1.0 in order to prevent the coextraction of vanadium impurities. Since iron(III) also extracts under these conditions, the leach liquor is reduced with metallic iron prior to extraction to convert any iron(III) present to the iron(II) state.

The extraction of uranium(VI) by D2EHPA has been shown[115] to proceed according to the stoichiometry

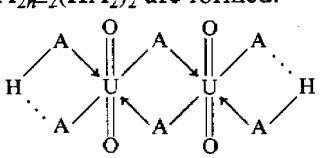
$$UO_2^{2+} + \overline{2H_2A_2} \longrightarrow \overline{UO_2(HA_2)_2} + 2H^+ \qquad (20)$$

Various structures have been proposed for the extracted complex, the most acceptable being (**11**), which was proposed originally by Baes.[75]



(**11**)

The dimeric complex $(UO_2)_2A_2(HA_2)_2$, reported to be present at low acidities,[117] can be formulated similarly (structure **12**). At high concentrations of uranium, polymers of increasingly long chains and of composition $(UO_2)_nA_{2n-2}(HA_2)_2$ are formed.[118]



(**12**)

In the Dapex process, uranium is usually stripped from the loaded organic phase with a solution of sodium carbonate, which converts the extractant to the sodium salt form, while retaining uranium in solution as sodium uranyl tricarbonate:

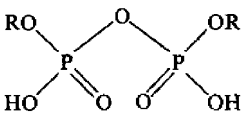
$$\overline{UO_2(HA_2)_2} + 3Na_2CO_3 \longrightarrow \overline{2NaHA_2} + Na_4UO_2(CO_3)_3 \qquad (21)$$

Sufficient tri-*n*-butyl phosphate (TBP) or isodecanol is incorporated into the organic phase to prevent separation of the sodium salt of D2EHPA as a third phase. Uranium is precipitated from the strip solution by the addition of magnesium oxide or ammonia gas to give a product known as 'yellow cake'.

On some plants,[71,114] vanadium is recovered from the barren aqueous phase emanating from the uranium-extraction circuit by the extraction of VO^{2+} into a solution of D2EHPA (usually a more concentrated solution than that used for the extraction of uranium) at an equilibrium pH value of about 2.2. The extracted complex has been shown to possess the stoichiometry $VO(HA_2)_2$ when an excess amount of the extractant is present.[80,119] ESR data are consistent with a five-coordinate structure of C_{4v} symmetry, and indicate that polymeric complexes, presumably of the type $(VO)_nA_{2n-2}(HA_2)_2$, are formed at high metal loadings.[80] Vanadium is recovered commercially from loaded organic phases by stripping with sulfuric acid. The strip solution is heated with sodium chlorate, and ammonia is added to precipitate the vanadium as 'acid red cake' (probably HVO_3), which is then treated in a fusion furnace to give the final product, 'black oxide'.

Organophosphorus acid extractants have found considerable use in recent years for the recovery of uranium as a byproduct in the manufacture of 'wet-process' phosphoric acid. This acid is obtained by the digestion of phosphate rock with sulfuric acid, and typically contains 0.1 to 0.2 g of uranium per litre.[120] It has been estimated that, in 1976, the wet-process acid produced in the USA alone contained some 2500 t of dissolved uranium;[121] this therefore represents a valuable potential source of this strategic metal.

Although solvent-extraction processes were operated at two phosphoric acid plants in Florida as long ago as the early 1950s, these were shut down a few years later when uranium became available at low cost from the sandstone deposits of the western USA. The process operated by the International Minerals and Chemical Corporation plant, for example, used a 5–7% solution of diisodecyl pyrophosphate (**13**; R = i-$C_{10}H_{21}$) in kerosene to extract uranium(IV) from phosphoric acid solutions that had been reduced with metallic iron.[120,122] The loaded organic phase was treated with 25% sulfuric acid to remove coextracted calcium (as $CaSO_4$), and the uranium was then stripped with a mixture of 20–25% sulfuric acid and 15–20% hydrofluoric acid to precipitate $UF_4 \cdot xHF$ ('green salt'). Although the product was not of high purity and serious losses of the extractant occurred due to hydrolysis, one of the new-generation plants in the USA is reported to be operating an essentially similar process based on the use of dioctyl pyrophosphate.[68] Some recent research has been directed towards improvement of the basic process.[123]



(13)

Conflicting information has been published on the relative extents of extraction of U^{4+} and UO_2^{2+} by dioctyl pyrophosphate.[120,124] The reduction of the feed acid, which is done in the commercial process, may serve mainly to minimize the coextraction of iron(III), which is extracted much more strongly than iron(II).[124] The uranium(IV) complexes extracted by dialkyl pyrophosphate have been reported to be of the type $U(R_2HP_2O_7)_4$,[125] and those of uranium(VI) to be of the type $UO_2(R_2P_2O_7)$.[124] However, some doubt was subsequently cast on these conclusions when it was found that the dioctyl pyrophosphate used, which had been prepared by the action of octanol upon phosphorus pentoxide, was a complex mixture of products.[126,127] Indeed, the strong extractive power of this reagent towards uranium(IV) appears to be the result of a fortuitous synergistic interaction between the components of the mixture.[126]

The Oak Ridge National Laboratory has developed two improved processes for the recovery of uranium from wet-process phosphoric acid and, since the dramatic increase in uranium prices in the mid-1970s, these are currently used widely on a commercial scale.[68] Both processes consist of two distinct cycles of extraction that are used to maximize the purification and concentration of the uranium present in the feed acid. In one process,[128] a mixture of the mono- and di-octylphenyl esters of orthophosphoric acid (as a 0.3 M solution in kerosene) is used in the first cycle to extract U^{4+} after the reduction of any UO_2^{2+} present in the feed with metallic iron. Uranium is recovered from the loaded organic phase by an oxidative stripping process using sodium chlorate in 12 M phosphoric acid. Uranium(VI), which is much less strongly extracted than U^{4+}, returns to the aqueous phase and, by the use of suitably high organic:aqueous ratios in the extraction and stripping circuits, can be concentrated to about 12 g l^{-1}. In the second process,[129] a mixture of D2EHPA (0.5 M) and tri-*n*-octylphosphine oxide (TOPO, 0.125 M) in kerosene is used in the first cycle to extract UO_2^{2+} after oxidation of the feed solution with sodium chlorate, hydrogen peroxide, or air. The mixed extractant shows a specific synergistic enhancement of extraction for UO_2^{2+}, and the loaded organic phase can be stripped by being contacted with a portion of the raffinate acid, the natural iron content of which has been partly reduced to Fe^{2+} with scrap iron. The equilibrium

$$UO_2^{2+} + 2Fe^{2+} + 4H^+ \rightleftharpoons U^{4+} + 2Fe^{3+} + 2H_2O \qquad (22)$$

is displaced to the right by virtue of the strong complexation of Fe^{3+} by phosphoric acid. Uranium(IV) is less strongly extracted by the mixed extractant than uranium(VI) and returns to the aqueous phase.

Both process alternatives use a second cycle of extraction of UO_2^{2+} by 0.3 M D2EHPA plus 0.075 M TOPO in kerosene. Uranium is stripped from the loaded organic phase with a solution of ammonium carbonate (2 to 3 M), which converts the D2EHPA to the ammonium salt form

and precipitates uranium in the aqueous phase as ammonium uranyl tricarbonate:

$$\overline{UO_2(HA_2)_2(TOPO)_n} + 3(NH_4)_2CO_3 \longrightarrow \overline{2NH_4(HA_2)} + (NH_4)_4UO_2(CO_3)_3 + \overline{n\text{TOPO}} \quad (23)$$

The precipitate is filtered and then calcined at 600 °C to yield high-grade U_3O_8. Alternatively, stripping with a more dilute solution of ammonium carbonate allows the uranium to remain in solution in the strip liquor and to be precipitated subsequently as $UO_4{\cdot}2H_2O$ by the addition of hydrogen peroxide.[130]

The chemistry of the extraction of UO_2^{2+} by mixtures of organophosphoric acids and neutral organophosphorus compounds has been the subject of many studies, and the available information has been widely discussed.[75,118,127,131–134] There is no general agreement on the mechanism of the synergistic effect, although an 'addition process' such as

$$\overline{UO_2(HA_2)_2} + \overline{TOPO} \longrightarrow \overline{UO_2(HA_2)_2{\cdot}TOPO} \quad (24)$$

appears to be favoured more than a 'substitution process' such as

$$\overline{UO_2(HA_2)_2} + \overline{2TOPO} \longrightarrow \overline{UO_2A_2(TOPO)_2} + \overline{H_2A_2} \quad (25)$$

In the addition mechanism, the coordination number of uranium is increased from six to seven, whereas in the substitution mechanism, there is no increase in the coordination number. The absence of any synergistic effect for uranium(IV) and thorium(IV),[127] which give coordination-saturated complexes $M(HA_2)_4$ with organophosphoric acids in which the metal ions are eight coordinate, is in accord with the addition mechanism.

The magnitude of the synergistic effect for UO_2^{2+} increases with increasing basicity of the phosphoryl oxygen of the neutral additive,[118] *viz.* $(RO)_3PO < (RO)_2RPO < (RO)R_2PO < R_3PO$. Other aspects of the extraction of uranium(VI) by mixtures of organophosphorus acids and neutral organophosphorus compounds have been discussed by Baes[75] and by Blake *et al.*[118]

In contrast to the chemistry of extraction of uranium(VI) by organophosphorus acids, that of uranium(IV) has not been widely studied. It is known,[135] however, that the extraction of U^{4+} by mono(2-ethylhexyl)phosphoric acid (2-ethylhexyl dihydrogen phosphate), for example, exceeds that of UO_2^{2+} by a factor of 10^5. This clearly provides the basis for the strong extraction of uranium(IV) from phosphoric acid solutions by extractants containing monoalkyl phosphates. The existence of a synergistic effect in the extraction of uranium(IV) by mixtures of mono(2-ethylhexyl)phosphoric acid and neutral organophosphorus compounds was also reported recently.[136]

Organophosphorus acid extractants have also been used commercially to recover thorium from barren solutions obtained from uranium ion-exchange plants. For instance, Rio Tinto Dow Ltd of Canada installed a plant at Elliot Lake in 1959 to extract thorium(IV) from solutions containing only 0.15 g of thorium per litre.[137] The loaded organic phase is stripped with 5 M sulfuric acid, from which the product subsequently crystallizes as an acid thorium(IV) sulfate.

It has been shown that the extraction of thorium(IV) by organophosphoric acids involves the mechanisms

$$Th^{4+} + \overline{3H_2A_2} \longrightarrow \overline{ThA_2(HA_2)_2} + 4H^+ \quad (26)$$

and

$$ThX^{3+} + \overline{3H_2A_2} \longrightarrow \overline{ThX(HA_2)_3} + 3H^+ \quad (27)$$

where X^- is the anion present in the aqueous phase. The extent of extraction of the anion-containing species depends upon the nature of the anion, the nature and concentration of the extractant, and the acidity of the aqueous phase.[138] A solid compound of the limiting stoichiometry ThA_4 was obtained by the contacting of organic solutions of D2EHPA with an excess amount of an aqueous solution of thorium(IV) chloride, whereas, in corresponding experiments with thorium(IV) nitrate, a solid of composition $Th(NO_3)A_3$ was obtained.[139] IR spectroscopy confirmed that the nitrate ion is covalently bonded to the metal.

Among other metals extracted commercially by D2EHPA, indium and thallium may be mentioned. Indium is recovered as a byproduct of copper smelting at Cerro del Pasco in Peru,[140] while indium and thallium are both recovered by solvent extraction on zinc plants in the USSR.[141] The extraction of indium(III) is reported to follow the stoichiometry

$$In^{3+} + \overline{3H_2A_2} \longrightarrow \overline{In(HA_2)_3} + 3H^+ \quad (28)$$

although oligomeric complexes such as $[InA(HA_2)_2]_2$ are formed at high metal loadings.[142] The extraction of thallium(III) is reported to proceed according to the reaction[143]

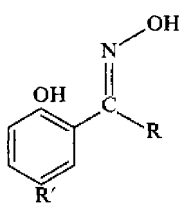
$$TlOH^{2+} + \overline{2H_2A_2} \longrightarrow \overline{TlA_3{\cdot}HA} + 2H^+ + 2H_2O \quad (29)$$

63.3.2.3 Solvent extraction of copper and nickel by ortho*-hydroxyoximes*

Since the mid-1960s, solvent extraction has been applied on a commercial scale to the recovery of copper from aqueous solutions obtained from the leaching of acid-soluble copper ores with dilute sulfuric acid. At present, several plants producing up to 200 t of copper per day by an integrated leach–solvent extraction–electrowinning route are in operation throughout the world.[37,144–146] All the plants in operation use extractants of the *ortho*-hydroxyoxime type, the active component being the *anti* isomer (**14**), in which R = alkyl, phenyl or hydrogen, and R′ = alkyl. These reagents (HA, where H denotes the replaceable, phenolic proton) extract copper by a pH-dependent cation-exchange mechanism:

$$Cu^{2+} + \overline{2HA} \longrightarrow \overline{CuA_2} + 2H^+ \qquad (30)$$

This allows the efficient extraction of copper at low acidities (usually at a pH value between 1.5 and 2.0) and its subsequent back-extraction (stripping) into an aqueous phase of higher acidity with simultaneous regeneration of the free hydroxyoxime for recycle to the extraction stage. Aqueous feeds to the extraction process typically contain 1 to 3 g of copper per litre and 5 to 25 g of iron per litre, as well as other impurities such as aluminum, magnesium and smaller amounts of nickel, cobalt, manganese, zinc and molybdenum. Copper is selectively extracted into a solution of an *ortho*-hydroxyoxime in a hydrocarbon diluent, and the barren aqueous phase (raffinate) containing the iron and other impurities is recycled to the leaching operation so that the acid liberated in the solvent-extraction step can be utilized. The copper contained in the loaded organic phase is then stripped into an acidic solution comprising the spent electrolyte from the copper-electrowinning cells. Thus the acid generated during electrowinning is used to reverse the reaction shown in equation (30). In addition to the purification of the copper-containing leach liquor, considerable concentration of the original copper content is achieved during the solvent-extraction process by the use of a high organic:aqueous ratio during stripping, thus producing a sufficiently concentrated aqueous solution of copper (about 50 g l^{-1}) for efficient electrowinning.



(**14**)

The extraction of some common metal ions by the model compound *anti*-1-(2-hydroxy-5-methylphenyl)octan-1-one oxime (**14**; R = *n*-C_7H_{15}, R′ = Me) is shown in Figure 10. The order of extraction of some common metals ($pH_{0.5}$ values in parentheses) is[147] Cu^{2+} (1.0) > Fe^{3+} (2.4) > Ni^{2+} (4.0) > Co^{2+} (6.1) > Zn^{2+} (7.4) > Mn^{2+} (8.8).

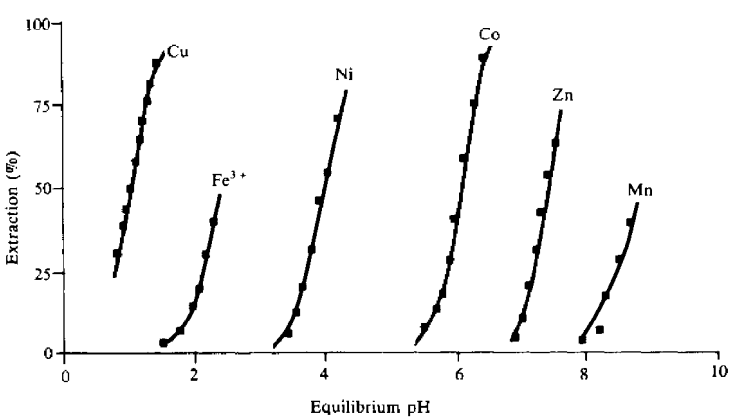
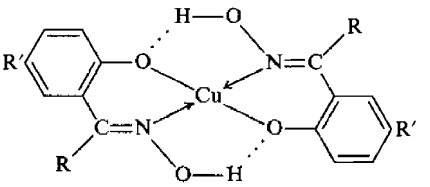


Figure 10 Extraction of some divalent metals and iron(III) (0.01 M as nitrates) from 0.2 M ammonium nitrate by 0.10 M solutions of *anti*-1-(2-hydroxy-5-methylphenyl)octan-1-one oxime in xylene at 30 °C

For the divalent metals, the order is largely as expected from the Irving–Williams series of stability constants. A similar extraction order has been reported for solutions of salicylaldoxime (**14**; R = R′ = H) in benzene, although the extraction of zinc(II) was found to be anomalously

low.[148] More recently[149], the order of extraction by solutions of the commercial reagent LIX 64N (**14**; R = Ph, R′ = C_9H_{19}) was given as Cu > Fe^{III} > Ni > Zn > Co.

The selectivity of these reagents for copper(II) over iron(III), which is an important aspect of their successful commercial acceptance, is attributable to the fact that the former metal gives a specifically structured, essentially square-planar complex of the type (**15**).[150]



(**15**)

In addition to the two six-membered rings formed by the chelation of the *ortho*-hydroxyoxime group to the central metal ion, this complex contains two five-membered rings formed by hydrogen bonding of the oximic hydrogens to the phenolic oxygens of the other ligand. This results in the unusual situation that the formation constant of the 2:1 complex (K_2) greatly exceeds that of the 1:1 complex by virtue of the additional stabilization of the former by the formation of the five-membered rings, which can occur only when both ligands are coordinated to the metal ion.[151] In contrast, the tris(salicylaldoximato)iron(III) complex is octahedral in structure, and no such extended planar ring formation is possible between the three oxime ligands. As a result, it appears that the stability of the iron(III) complex is actually less than that of the copper(II) complex, which enables the extraction of copper to be carried out at pH values lower than those required for the efficient extraction of iron.

It should be noted that, since the extraction of iron(III) by *ortho*-hydroxyoximes shows a third-order dependence on the concentration of the extractant[152]

$$Fe^{3+} + \overline{3HA} \longrightarrow \overline{FeA_3} + 3H^+ \qquad (31)$$

in contrast to the second-order dependence for copper(II) (equation 30), decreasing selectivities for copper over iron are to be expected as the concentration of the extractant is increased. However, owing to the different rates of extraction of copper(II) and iron(III),[152,153] the selectivity for copper can be enhanced by the use of short phase-contact times.

In the solid state, the metal atoms in bis(salicylaldoximato)copper(II) show two additional contacts with the oxime oxygens of adjacent molecules, resulting in a distorted octahedral structure. However, the axial Cu—O distance (2.66 Å) is much longer than the metal–ligand distances in the square-planar array (Cu—O, 1.92 Å and Cu—N, 1.94 Å).[154] Studies by ESR of copper(II) extracts of the commercial reagent SME 529 (**14**; R = Me, R′ = C_9H_{19}) have shown that the copper complex exists as a square-planar species in hydrocarbon solutions, but that five-coordinate adducts are formed in the presence of ammonia or pyridine.[155]

Spectrophotometric evidence suggests that the nickel(II) and palladium(II) complexes of salicylaldoxime are analogous to that of copper(II) and that they contain a *trans* square-planar N_2O_2 donor set, whereas the complexes of cobalt(II), zinc(II), iron(II) and manganese(II) contain a *cis* square-planar N_2O_2 donor set.[150] The anomalous stability of the iron(II)[150] complex in the series ($\log\beta_2$ in 75% (v/v) dioxane at 25 °C, shown in parentheses),[151] Cu(21.5) > Fe(16.7) > Ni(14.3) > Co(13.5), Zn(13.5) > Mn(11.9), cannot be explained in terms of spin pairing in the iron(II) complex, which shows a paramagnetism equivalent to four unpaired electrons.[156] It has been suggested, on the basis of Mössbauer spectroscopic measurements, that metal-to-ligand back-coordination by π-bond formation occurs, the third ionization potential of iron being lower than that of any of the other metals studied.[156]

Bis(salicylaldoximato)nickel(II) is diamagnetic in the solid state, but becomes partially paramagnetic in solution in chloroform[157] and aqueous dioxane.[151] This is likely to be due to molecular association or solvation,[158] rather than to the adoption of a distorted tetrahedral structure in solution.[151] The nickel(II) complex readily forms pseudo-octahedral bis-adducts in the presence of large amounts of amines,[159,160] although analogous complexes of commercial *ortho*-hydroxyoximes have been reported to retain the square-planar structure in hydrocarbon solution in the presence of moderate amounts of ammonia or aliphatic amines.[161]

A relatively small number of commercial operations, such as those of the SEC Corporation at El Paso, Texas,[162] and of the Nippon Mining Company at Hitachi, Japan,[163] use *ortho*-hydroxyoximes for the recovery of nickel. In the SEC Corporation process, the aqueous feed solution consists of a crystallizer discharge stream from a local copper refinery, and contains about 70 g of copper

and 20 g of nickel per litre. After the solvent extraction of copper at a pH value of 1.6 to 2.2, the pH value of the solution is raised to between 8.5 and 10 with ammonia gas, and nickel is extracted into a 9% solution of LIX 64N. A complete description of the process has been given.[164]

In the Nippon Mining Company process,[163] the aqueous feed consists of a solution of cobalt, nickel and other metal sulfates obtained by the high-pressure oxidative leaching of a mixed metal sulfide ore. Following the removal of iron and copper by chemical precipitation methods, and the successive extraction of zinc and cobalt by organophosphorus acid reagents (Section 63.3.2.2) under weakly acidic conditions, the pH value of the solution is adjusted to between 9 and 9.5 with ammonia, and nickel is extracted into a 25% solution of LIX 64N in an alkane solvent.

Although it is clear from Figure 3 that *ortho*-hydroxyoximes are able to extract nickel under mildly acidic conditions (a pH value of 4 to 5), the attainment of equilibrium is slow, at least 1 h of phase contacting being required at moderate stirring speeds. The extraction rate shows an inverse first-order dependence on the hydrogen ion concentration,[165] however, hence much shorter mixing times are adequate under the ammoniacal conditions used in commercial processes.

The marked tendency for cobalt(II) to become oxidized to cobalt(III) after its extraction by hydroxyoximes is well known, and results from the large decrease in redox potential of the Co^{2+}/Co^{3+} couple in the presence of nitrogen donor ligands

$$[Co(H_2O)_6]^{2+} \longrightarrow [Co(H_2O)_6]^{3+} + e^- \quad E^\circ\ 1.84\ V \tag{32}$$

and

$$[Co(NH_3)_6]^{2+} \longrightarrow [Co(NH_3)_6]^{3+} + e^- \quad E^\circ\ 0.1\ V \tag{33}$$

Stripping of the extracted cobalt(III) complexes from the organic phase is very difficult, even with concentrated solutions of mineral acids, presumably because of the slow kinetics of ligand exchange of the d^6 ion. The slow ligand exchange of cobalt(III) complexes can be used to advantage in the separation of cobalt and nickel, however. If an ammoniacal solution of nickel(II) and cobalt(II) is aerated sufficiently for the latter to be oxidized to cobalt(III) before being contacted with an organic solution of an *ortho*-hydroxyoxime,[166] nickel can be extracted with high selectivity owing to its much faster reaction kinetics. Indeed, with aliphatic hydroxyoximes, no appreciable extraction of the species $[Co(NH_3)_6]^{3+}$, $[Co(NH_3)_5(H_2O)]^{3+}$ and $[Co(NH_3)_4(H_2O)_2]^{3+}$ was found during contact periods of several days.[167]

The commercial extraction of palladium(II) by *ortho*-hydroxyoximes is discussed in Section 63.3.2.5; here, it need be noted only that palladium(II) is extracted by these reagents at pH values considerably lower than those required for the extraction of copper(II).

The kinetics of the extraction of metals, especially copper(II), by *ortho*-hydroxyoximes (HA) has been widely studied in recent years.[146] Of particular interest is the observation that the rate of extraction can be considerably increased by the incorporation of small amounts of aliphatic α-hydroxyoximes (H_2B) into the organic phase.[168] An even more marked effect has been noted with α-dioximes.[169,170] Accelerator compounds of the former type are used in Henkel's commercial extractant LIX 64N, whereas those of the latter type are used in the Shell reagent SME 530.

Although the accelerator compounds can form copper complexes at sufficiently high pH values,[167,171] it is unlikely that the catalytic action operates by a simple exchange mechanism such as

$$Cu^{2+} + \overline{2H_2B} \longrightarrow \overline{Cu(HB)_2} + 2H^+ \tag{34}$$

$$\overline{Cu(HB)_2} + \overline{2HA} \longrightarrow \overline{CuA_2} + \overline{2H_2B} \tag{35}$$

since the catalysis is still operative at pH values below which reaction (34) takes place to any significant extent, particularly for the α-hydroxyoximes.[170] It is more likely that the catalysis involves the transient formation of mixed complexes of the type CuA(HB), of stability intermediate between those of the complexes $Cu(HB)_2$ and CuA_2:

$$Cu^{2+} + \overline{HA} \longrightarrow CuA^+ + H^+ \tag{36}$$

$$CuA^+ + \overline{H_2B} \longrightarrow \overline{CuA(HB)} + H^+ \tag{37}$$

$$\overline{CuA(HB)} + \overline{HA} \longrightarrow \overline{CuA_2} + \overline{H_2B} \tag{38}$$

By this means, the reaction

$$CuA^+ + \overline{HA} \longrightarrow \overline{CuA_2} + H^+ \tag{39}$$

which is the rate-determining step in the absence of H_2B[172] (probably owing to the need for specific orientation requirements at the organic–aqueous interface), is largely replaced by reaction (37), in which the relatively fast formation of a five-membered ring is involved, and reaction (38), in which the second six-membered ring and hydrogen-bonded bridged structure is formed under homogeneous conditions by ligand exchange in the organic phase. It is probably also relevant that the hydrogen-bonded bridged structure is absent in the mixed complex CuA(HB).

The kinetics of the homogeneous reaction between copper(II) and *ortho*-hydroxyoximes were also studied in detail recently.[173]

63.3.2.4 Solvent extraction of base metals by amine salts

Amine salts represent the only commercially important class of extractants of the anion-exchange type. Their most widespread use is in the extraction of uranium from sulfate leach liquors, but they have found application in the recovery of cobalt, zinc and copper from chloride solutions, as well as in the extraction of metals that readily form oxyanions, such as vanadium, molybdenum and tungsten.

The order of preference of alkylammonium cations for simple inorganic anions in exchange reactions of the type

$$\overline{R_3NHX} + Y^- \longrightarrow \overline{R_3NHY} + X^- \qquad (40)$$

lies in the sequence[174–176] $ClO_4^- > NCS^- > I^- > NO_3^- > Br^- > Cl^- > SO_4^{2-} > F^-$. This sequence is largely a reflection of the readiness with which the anions leave the aqueous phase. Small, strongly polarizing anions such as F^- are strongly hydrated, and it is much less energetically favourable for them to leave the aqueous phase than it is for the larger anions of more diffuse charge, such as ClO_4^-. According to the same principles, complex metallic anions such as $FeCl_4^-$, $[UO_2(SO_4)_2]^{2-}$ and $Co(NCS)_4^{2-}$ should be readily extracted in the absence of competition from strongly extracted simple inorganic anions.

The formation of the extractable ion-pair is not dependent solely on electrostatic interactions, but may also involve hydrogen bonds of the type $R_3N^+H\cdots Cl^-$, for example.[175] Therefore the extraction of a given anion by different amines follows the order[177,178] primary > secondary > tertiary > quaternary, owing to the decreasing availability of interacting hydrogens bound to the nitrogen atom, as well as the increasing steric hindrance of the substituent alkyl groups to the approach of the extracted anion. In contrast, complex anions, such as halometallates, are incapable of forming hydrogen bonds with the alkylammonium cations, and therefore compete most effectively with the corresponding free halide ions in the order[175] quaternary > tertiary > secondary > primary, which is the observed order of extraction efficiency for most metals from chloride solutions.[179]

The order of extractability of different metals from chloride solutions by a given amine is usually that expected from the tendency of each metal to form anionic chloro complexes.[180] This is evident in Figure 11, which shows the extraction of several metals from lithium chloride solutions by 0.50 M solutions of the tertiary amine Alamine 336 in xylene. The order of extraction,[181] $Pd^{II} > Cd^{II} > Zn^{II} > Fe^{III} > Cu^{II} > Co^{II} > Mn^{II} > Fe^{II} \gg Ni^{II}$, is in qualitative agreement with the order of the stability constants of the corresponding chlorometallate anions,[182,183] although it is difficult to predict the position of some of the metals that form rather weak complexes, such as cobalt, manganese and iron(II). It appears, therefore, that the extractability of a given metal is more a reflection of the stability of the anionic metal species

$$M^{2+} + 4Cl^- \longrightarrow MCl_4^{2-} \qquad (41)$$

than of the relative affinity of the complex anion for the alkylammonium cation of the extractant, *e.g.*

$$\overline{2R_3NHX} + MCl_4^{2-} \longrightarrow \overline{(R_3NH)_2MCl_4} + 2X^- \qquad (42)$$

Spectral investigations of the organic extracts of amine salts from metal chloride solutions are consistent with the extraction of tetrahedral tetrachlorometallate anions for metals such as Fe^{III}, Cu^{II}, Zn^{II}, Cd^{II}, Co^{II} and Mn^{II}.[184–186] Analysis of the metal-saturated organic phases reveals the expected ratio of amine:metal:chloride of 2:1:4 for the divalent metals and 1:1:4 for the trivalent metals. The extractability of the tetravalent actinides also follows the order of the tendency of those metals to form anionic chloro complexes, and the spectra of the organic extracts are those expected for the octahedral MCl_6^{2-} species.[187]

The analysis of the distribution data is also in agreement with extraction stoichiometries such as

$$\overline{2R_3NHCl} + MCl_4^{2-} \longrightarrow \overline{(R_3NH)_2MCl_4} + 2Cl^- \quad (43)$$

$$\overline{R_3NHCl} + MCl_4^- \longrightarrow \overline{R_3NHMCl_4} + Cl^- \quad (44)$$

and

$$\overline{2R_3NHCl} + MCl_6^{2-} \longrightarrow \overline{(R_3NH)_2MCl_6} + 2Cl^- \quad (45)$$

Deviations from such stoichiometries may indicate the formation of mixed associates of the quadrupole type,[127,188] such as $[R_3NH^+MCl_4^-\ R_3NH^+Cl^-]$, and evidence has been given for the formation of species of this stoichiometry for zinc(II)[189,190] and for copper(II) and cobalt(II).[190]

It can be seen from Figure 11 that, by the appropriate choice of the equilibrium concentration of chloride ion in the aqueous phase, separations between certain pairs of metals can be made, for example between copper(II) and manganese(II) at a chloride concentration of 3.0 M, and between cobalt(II) and nickel(II) at a chloride concentration of 6 to 8 M. Furthermore, the metals can be stripped from the loaded organic phase by being contacted with an appropriate volume of water so that the equilibrium concentration of chloride ion in the strip liquor lies on the lower portion of the extraction curve, where substantial aquation of the extracted chlorometallate occurs

$$\overline{(R_3NH)_2MCl_4} + 6H_2O \longrightarrow M(H_2O)_6^{2+} + 2Cl^- + \overline{2R_3NHCl} \quad (46)$$

and the metal cation returns to the aqueous phase. Thus, for example, copper(II) can be stripped from 0.50 M solutions of Alamine 336 in xylene at equilibrium concentrations of chloride below about 2 M, and cobalt(II) at below about 4 M.

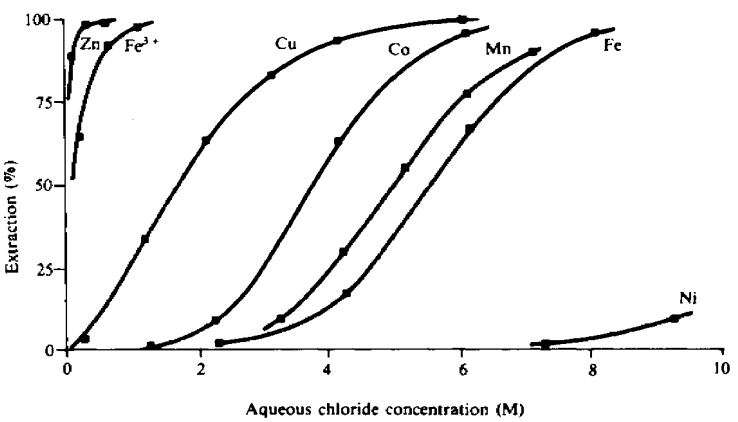


Figure 11 Extraction of some divalent metals and iron(III) (0.10 M as chlorides) from solutions of lithium chloride containing 0.10 M hydrochloric acid by 0.50 M solutions of Alamine 336 (commercial tri-*n*-octylamine hydrochloride) in xylene at 20 °C

Such principles are used in several commercial processes for the separation of metals in chloride media. At the Falconbridge Nikkelverk in Kristiansand, Norway, a solution derived from the leaching of a nickel–copper matte in 8 M hydrochloric acid is processed by solvent-extraction techniques.[191,192] The solution, containing 120 g of nickel per litre and about 2 g each of iron, cobalt and copper per litre, is first extracted with TBP to remove the iron (see Section 63.3.2.6). Cobalt and copper are then coextracted into a 10% solution of triisooctylamine in an aromatic diluent in three countercurrent contacting stages. The metals are separated by selective stripping with water: cobalt first, at an organic:aqueous ratio of 30:1, and then copper at an organic:aqueous ratio of 20:1. The nickel chloride in the raffinate from solvent extraction is recovered by crystallization, and is converted to NiO in a fluidized-bed reactor using naphtha gas at 850 °C. Reduction with hydrogen at 600 °C gives a nickel metal product containing only 5 μg each of cobalt and copper per gram. Alternatively, pure nickel can be recovered directly from the nickel chloride solution by electrowinning.

At the Société le Nickel refinery in Le Havre, France,[193] a solution obtained from the leaching of a chlorinated nickel slag and containing 56 g of nickel, 22 g of cobalt and 36 g of iron per litre in 7.5 M chloride is first treated with a 0.3 M solution of the secondary amine Amberlite LA-2 in an aromatic solvent to remove the iron:

$$\overline{R_2NH_2Cl} + FeCl_4^- \longrightarrow \overline{R_2NH_2FeCl_4} + Cl^- \quad (47)$$

Cobalt is then extracted into a 0.3 M solution of the tertiary amine Adogen 381 in an aromatic diluent:

$$\overline{2R_3NHCl} + CoCl_4^{2-} \longrightarrow \overline{(R_3NH)_2CoCl_4} + 2Cl^- \quad (48)$$

The Sumitomo Metal Mining Co. in Japan uses a 40% solution of tri-*n*-octylamine in xylene to separate cobalt and nickel in chloride media.[44,163,194] The traces of zinc that are present are coextracted with the cobalt and, owing to the strong extraction of zinc, remain in the organic phase when the cobalt is stripped with water (*cf.* Figure 11). The zinc is then removed from a 'bleed stream' of the organic phase by 'deprotonation stripping' with sodium hydroxide solution:

$$\overline{(R_3NH)_2ZnCl_4} + 4NaOH \longrightarrow \overline{2R_3N} + Zn(OH)_2 + 4NaCl + 2H_2O \quad (49)$$

The precipitated zinc(II) hydroxide is removed by filtration, and the zinc-free organic phase is recycled to the extraction circuit after conversion to the chloride form with hydrochloric acid.

Secondary amine extractants are used for the recovery of zinc from liquors obtained by the leaching of pyrite cinders at the Metalquímica del Nervion plant in Bilbao, Spain,[69] and at the Quimigal plant near Lisbon, Portugal.[91] Traces of other metals that also form chloro anions, such as copper, cadmium and iron(III), are also extracted, and both plants use a second extraction cycle with D2EHPA to further purify the zinc solution prior to electrowinning.

The use of amine salts in the commercial solvent extraction of the platinum-group metals from chloride solutions is described in Section 63.3.2.5.

By far the most important use of amine salt extractants is in the recovery of uranium from acidic leach liquors. The basic process was developed at the Oak Ridge National Laboratory in the USA,[195] and essentially similar processes are currently in operation throughout the world. Examples of plant practice in the USA,[196] Canada,[197] Australia,[198] South Africa[199,200] and South West Africa[201] have been described.

Solvent extraction is applied either directly to the weakly acidic leach liquor (the method is known as the Purlex process in South Africa, and the Amex process in the USA) or to the strongly acidic eluate obtained from a preliminary ion-exchange treatment of the leach liquor (known as the Bufflex process in South Africa, and the Eluex process in the USA). In the Purlex process, a 5% solution of a tertiary amine in kerosene is typically used to treat a leach liquor containing up to 1 g of uranium per litre (although concentrations as low as 0.04 g l^{-1} may be encountered) at a pH value of 1 to 2. A modifier such as isodecanol (2–5%) is usually incorporated into the organic phase to prevent the formation of a third phase and to inhibit the formation of an emulsion. The extraction of uranium(VI) is usually considered to proceed according to reactions such as[202]

$$\overline{(R_3NH)_2SO_4} + UO_2(SO_4)_2^{2-} \longrightarrow \overline{(R_3NH)_2UO_2(SO_4)_2} + SO_4^{2-} \quad (50)$$

and

$$\overline{2(R_3NH)_2SO_4} + UO_2(SO_4)_3^{4-} \longrightarrow \overline{(R_3NH)_4UO_2(SO_4)_3} + 2SO_4^{2-} \quad (51)$$

Experiments with ^{35}S-labelled sulfate solutions have shown that part of the extracted uranium is transferred across the interface as the neutral species UO_2SO_4, especially at low concentrations of aqueous sulfate;[203] the principal extraction reactions for the secondary amine used, di-*n*-decylamine, are reported to be

$$\overline{3(R_2NH_2)_2SO_4} + UO_2(SO_4) \longrightarrow \overline{(R_2NH_2)_6UO_2(SO_4)_4} \quad (52)$$

and

$$2(\overline{3(R_2NH_2)_2SO_4} + UO_2(SO_4)_2^{2-} \longrightarrow \overline{(R_2NH_2)_6UO_2(SO_4)_4} + SO_4^{2-} \quad (53)$$

Some authors consider that the extracted complex is best formulated as an adduct, such as $[(R_3NH)_2SO_4]_2$, $UO_2SO_4(H_2O)_3$, which is the stoichiometry suggested by Sato on the basis of the analysis of solutions of tri-*n*-octylamine saturated with uranium.[204] Further studies of the extraction of uranium from sulfate media by amine salts have been reviewed by Cattrall and Slater.[205]

The extraction of uranium(VI) from sulfate media by amine sulfates of different types lies in the order tertiary > secondary > primary, whereas the extraction of iron(III) lies in the reverse order,[195,206] with the result that tertiary amines are the obvious choice for the selective extraction of uranium in the presence of iron.

Uranium can be stripped from the loaded organic phase with a variety of reagents, such as concentrated solutions of sodium chloride, ammonium sulfate, sodium carbonate or ammoniacal ammonium sulfate (equations 54–57).

$$\overline{(R_3NH)_4UO_2(SO_4)_3} + 4NaCl \longrightarrow \overline{4R_3NHCl} + Na_4UO_2(SO_4)_3 \quad (54)$$

$$\overline{(R_3NH)_4UO_2(SO_4)_3} + 2(NH_4)_2SO_4 \longrightarrow \overline{2(R_3NH)_2SO_4} + (NH_4)_4UO_2(SO_4)_3 \quad (55)$$

$$\overline{(R_3NH)_4UO_2(SO_4)_3} + 7Na_2CO_3 \longrightarrow \overline{4R_3N} + Na_4UO_2(CO_3)_3 + 3Na_2SO_4 + 4NaHCO_3 \quad (56)$$

$$\overline{(R_3NH)_4UO_2(SO_4)_3} + 4NH_3 \longrightarrow \overline{4R_3N} + (NH_4)_2SO_4 + (NH_4)_2UO_2(SO_4)_2 \quad (57)$$

Uranium is recovered from the strip liquor by the introduction of ammonia gas to precipitate ammonium diuranate:

$$2(NH_4)_2UO_2(SO_4)_2 + 6NH_3 + 3H_2O \longrightarrow (NH_4)_2U_2O_7 + 4(NH_4)_2SO_4 \quad (58)$$

Extractants of the amine type have been used extensively for the recovery of vanadium, which was among the first metals to be produced commercially by solvent-extraction techniques. Much of the world's production of this metal is obtained from the processing of such diverse materials as uranium ores, vanadiferous clays, phosphate rock, iron slags, titaniferrous magnetites and petroleum ashes. The potential application of solvent-extraction techniques to upgrade and purify dilute solutions of vanadium that had been derived from the leaching of such materials was recognized at an early stage and, in 1966, no less than 11 solvent extraction plants for the recovery of vanadium were already in operation in the USA.[207]

In a typical process, the vanadium ore is roasted with sodium chloride in the presence of air to produce sodium metavanadate:

$$V_2O_3 + 2NaCl + O_2 + H_2O \longrightarrow 2NaVO_3 + 2HCl \quad (59)$$

The calcine is leached with water, the pH value of the leach liquor adjusted to about 3 with sulfuric acid, and the vanadium is extracted into an organic solution of a tertiary amine salt. The main species present in the pH range 3 to 4 are $HV_{10}O_{28}^{5-}$ and $H_2V_{10}O_{28}^{4-}$,[208] and the ratio of the amine to the metal in organic phases saturated with vanadium[209] was found to be 1:2, in accordance with the mechanism

$$\overline{5R_3NH{\cdot}HSO_4} + HV_{10}O_{28}^{5-} \longrightarrow \overline{(R_3NH)_5HV_{10}O_{28}} + 5HSO_4^- \quad (60)$$

At very low concentrations of vanadium (less than 2×10^{-5} M) only monomeric metal species are present[209] and the extraction process can be expressed as

$$\overline{R_3NH{\cdot}HSO_4} + VO_3^- \longrightarrow \overline{R_3NHVO_3} + HSO_4^- \quad (61)$$

Vanadium is recovered from the loaded organic phase by stripping with an ammoniacal solution of ammonium sulfate, which results in the precipitation of the sparingly soluble ammonium metavanadate:

$$\overline{(R_3NH)_5HV_{10}O_{28}} + 10NH_4OH \longrightarrow \overline{5R_3N} + 10NH_4VO_3 + 8H_2O \quad (62)$$

The ammonium metavanadate is marketed as such, or calcined to vanadium(V) oxide:

$$2NH_4VO_3 \longrightarrow V_2O_5 + 2NH_3 + H_2O \quad (63)$$

Alternative stripping procedures using concentrated solutions containing chloride or nitrate ions to displace the vanadate from the loaded solvent, or sulfur dioxide to reduce the vanadium(V) to the oxovanadium(IV) cation have been proposed.[210]

Amine salts have been used for more than 25 years in the manufacture of pure ammonium paratungstate from sodium tungstate solutions obtained from the leaching of tungsten ores with alkali.[211] Such solutions are produced by the leaching of scheelite with sodium carbonate solution at 190 to 225 °C

$$CaWO_4 + Na_2CO_3 \longrightarrow Na_2WO_4 + CaCO_3 \quad (64)$$

or by the leaching of wolframite with sodium hydroxide solution at 110 to 130 °C

$$(Fe,Mn)WO_4 + 2NaOH \longrightarrow Na_2WO_4 + (Fe,Mn)(OH)_2 \quad (65)$$

Since the solvent-extraction process is not selective for tungsten over molybdenum, any of the latter metal present is removed by the addition of sodium sulfide at a pH value of about 10

$$MoO_4^{2-} + 4S^{2-} + 4H_2O \longrightarrow MoS_4^{2-} + 8OH^- \quad (66)$$

followed by acidification to a pH value between 2.5 and 3 in order to precipitate molybdenum trisulfide

$$MoS_4^{2-} + 2H_3O^+ \longrightarrow MoS_3 + H_2S + H_2O \quad (67)$$

In a typical solvent-extraction process,[211] the pH value of the sodium tungstate solution is adjusted to about 2.5 with sulfuric acid, and the tungsten is extracted into a 7% solution of the tertiary amine Alamine 336 plus 7% isodecanol in kerosene in two countercurrent stages at a temperature of 50 °C. Distribution data are consistent with the extraction of species such as $H_2W_{12}O_{40}^{6-}$ and $W_{12}O_{40}^{8-}$ in reactions of the type[208,212]

$$\overline{8R_3NHHSO_4} + W_{12}O_{40}^{8-} \longrightarrow \overline{(R_3NH)_8W_{12}O_{40}} + 8HSO_4^- \quad (68)$$

The loaded organic phase, containing 20–40 g of tungsten per litre, is washed with water to remove entrained sodium ions, and stripped with aqueous ammonia:

$$\overline{(R_3NH)_8W_{12}O_{40}} + 10NH_3 + H_2O \longrightarrow (NH_4)_{10}W_{12}O_{41} + \overline{8R_3N} \quad (69)$$

Ammonium paratungstate is recovered from the strip solution by evaporative crystallization, dried and calcined to produce 'blue oxide':[208]

$$(NH_4)_{10}W_{12}O_{41} \longrightarrow 12WO_3 + 10NH_3 + 5H_2O \quad (70)$$

Amine salts have been used to recover molybdenum from solutions arising from a variety of sources. Most of the western world's supply of this metal is derived from molybdenite (MoS_2) concentrates obtained as a byproduct of copper production in the USA and Chile. Such concentrates are roasted to molybdenum(VI) oxide (volatile Re_2O_7 can often be recovered as a valuable byproduct from the roaster gases) and leached with dilute sulfuric acid to remove the copper from the crude MoO_3 product. Some molybdenum also dissolves and can be recovered, for example, by the same technique as that practised at Kennecott's Utah Copper Division smelter,[213] *i.e.* by extraction into a solution of a tertiary amine in kerosene at an aqueous pH value of about 1.

Organic solutions of a tertiary amine saturated with molybdenum[214] were found to have an amine:metal ratio of 1:2. In accordance with the species known to be present in moderately acidic solutions of molybdenum(VI), the most probable mechanism of extraction is

$$\overline{4R_3NH^+HSO_4^-} + Mo_8O_{26}^{4-} \longrightarrow \overline{(R_3NH)_4Mo_8O_{26}} + 4HSO_4^- \quad (71)$$

Although no polynuclear molybdenum(VI) species containing less than seven metal atoms is known in aqueous solution,[215] this does not preclude the existence of such species in organic extracts, the observed amine:metal ratio also being consistent with the extraction of $Mo_4O_{13}^{2-}$ or $Mo_2O_7^{2-}$ species.

The technical-grade molybdenum(VI) oxide obtained as described previously can be further purified by solvent extraction as an alternative to the conventional sublimation method,[216,217] the molybdenum being brought into solution by leaching of the oxide with sodium hydroxide:

$$MoO_3 + 2NaOH \longrightarrow Na_2MoO_4 + H_2O \quad (72)$$

Acidification of the leach liquor with sulfuric acid produces solutions containing $Mo_8O_{26}^{4-}$, which is extracted into a solution of tertiary amine hydrogen sulfate as described previously. Loaded organic phases are stripped with aqueous ammonia to give solutions from which ammonium paramolybdate can subsequently be crystallized:

$$\overline{(R_3NH)_4Mo_8O_{26}} + 8NH_3 + 2H_2O \longrightarrow 4(NH_4)_2Mo_2O_7 + \overline{4R_3N} \quad (73)$$

Calcination of the ammonium paramolybdate yields molybdenum(VI) oxide of high purity:[208]

$$(NH_4)_2Mo_2O_7 \longrightarrow 2MoO_3 + 2NH_3 + H_2O \quad (74)$$

Molybdenum can also be recovered economically from some uranium leach liquors, particularly those of the USA. When uranium is stripped from amine extractants by solutions of sodium chloride, any molybdenum present remains in the organic phase, and can be subsequently recovered by being stripped into a solution of sodium carbonate. A process has been operated in which the strip liquor is acidified to a pH value of 4.5 and the molybdenum is reextracted into a solution of quaternary amine chloride in kerosene.[218] The extracted metal is stripped into a solution containing sodium hydroxide and sodium chloride to produce liquors containing 30–40 g of molybdenum per litre, from which calcium molybdate can be precipitated by the addition of calcium chloride.

63.3.2.5 Solvent extraction of platinum-group metals and gold

The traditional route for industrial separation of the platinum-group metals (PGM) comprises a complicated series of operations based largely on selective precipitations, often of low efficiency.[219–221] A multitude of solid–liquid separations and recycle operations are required. The

poor once-through yield of refined metals results in a high inventory of process intermediates, which is particularly undesirable in view of the high value of the final product. Solvent-extraction methods, with their potential for efficient separations and rapid throughput, were found to represent an attractive alternative to established refining procedures, and have been used by several major PGM refiners since the late 1970s.[222–227]

The chemistry of the PGM in aqueous chloride media (which are invariably used in their processing) is characterized by a strong tendency toward the formation of complex anions and by the slow rate of ligand-exchange reactions. Indeed, among the commonly encountered oxidation states of these metals, only palladium(II) is sufficiently labile for recovery by extraction processes based on ligand exchange to be of practical use. However, the slower rates of reaction of the remaining PGM, in particular platinum(II) and platinum(IV), probably contribute substantially to the selectivity towards palladium shown by extractants such as dialkyl sulfides[228] (R_2S, reaction 75) and *ortho*-hydroxyoximes (HL, reaction 76), which are used at the Acton plant of Inco Europe[226] and the Royston plant of Matthey Rustenburg Refiners[223-225] respectively. The use of dialkyl sulfides for the extraction of palladium (and gold) has also been patented in South Africa (equations 75 and 76).[229]

$$PdCl_4^{2-} + \overline{2R_2S} \longrightarrow \overline{Pd(R_2S)_2Cl_2} + 2Cl^- \tag{75}$$

$$PdCl_4^{2-} + \overline{2HL} \longrightarrow \overline{PdL_2} + 2H^+ + 4Cl^- \tag{76}$$

Even for palladium, contact times of at least 1 h are needed for these reactions to proceed substantially to completion, and the dialkyl sulfide extraction process is operated in a batch, rather than continuous, mode to accommodate this requirement. Gold(III), unless removed previously, is also extracted by dialkyl sulfides in the form of the complex $AuCl_3(R_2S)$, and silver(I) can be extracted from nitrate solutions as the complex $AgNO_3(R_2S)_2$.[228]

Interestingly, the extraction of palladium(II) by *ortho*-hydroxyoximes can be accelerated sufficiently to be used in a continuous process by the addition of small quantities of amine salts of high molecular mass to the organic phase.[230] Presumably these accelerator compounds operate by the initial extraction of palladium in a rapid anion-exchange process involving no ligand exchange

$$PdCl_4^{2-} + \overline{2RNH_3^+Cl^-} \longrightarrow \overline{(RNH_3^+)_2PdCl_4^{2-}} + 2Cl^- \tag{77}$$

followed by a relatively fast, homogeneous ligand-exchange reaction in the organic phase

$$\overline{(RNH_3^+)_2PdCl_4^{2-}} + \overline{2HL} \longrightarrow \overline{PdL_2} + \overline{2RNH_3^+Cl^-} + \overline{2HCl} \tag{78}$$

thus regenerating the amine salt for further catalysis. This mechanism therefore replaces the slow, heterogeneous (interfacial) direct reaction between the hydroxyoxime and tetrachloropalladate(II) ion that operates in the absence of the amine salt.

Laboratory-synthesized samples of hydroxyoximes of high purity have extremely slow extraction rates, as might be expected, since, in addition to the slow rate of ligand exchange of the metal ion, the formation of the chelate complex analogous in structure to that shown previously for copper(II) requires a specific orientation of the ligand at the organic–aqueous interface. Commercially produced samples of hydroxyoximes invariably have much faster extraction rates, probably because impurities are present, such as analogues of the extractant proper that are relatively water-soluble and have a lower molecular mass, as well as non-chelating oximes (B) that can form complexes of the type $PdCl_2B_2$[231] and thus accelerate the rate of metal extraction by the homogeneous reaction

$$\overline{PdCl_2B_2} + \overline{2HL} \longrightarrow \overline{PdL_2} + \overline{2B} + \overline{2HCl} \tag{79}$$

The back-extraction (stripping) of palladium is achieved in the hydroxyoxime process by contacting the loaded organic phase with a concentrated solution of hydrochloric acid (about 6 M), thus causing the reversal of reaction (76). Palladium can be recovered from the strip liquor by the addition of ammonia, and the precipitated $Pd(NH_3)_2Cl_2$ can be calcined to yield pure palladium metal. In the dialkyl sulfide process, however, the extraction reaction (75) is independent of acidity, and is therefore reversed by the use of aqueous ammonia, which forms a stable cationic complex with palladium(II):

$$\overline{Pd(R_2S)_2Cl_2} + 4NH_3 \longrightarrow Pd(NH_3)_4^{2+} + \overline{2R_2S} + 2Cl^- \tag{80}$$

Palladium is again recovered in the form of $Pd(NH_3)_2Cl_2$ by the addition of hydrochloric acid to the strip liquor.

The existence of the PGM and gold in the form of complex anions in chloride media has been used to advantage in the design of several solvent-extraction processes. Thus, metal–chloro complexes of the type MCl_x^{n-} can be extracted by, for example, salts of secondary amines:

$$\overline{nR_2NH_2^+Cl^-} + MCl_x^{n-} \longrightarrow \overline{(R_2NH_2^+)_nMCl_x^{n-}} + nCl^- \quad (81)$$

The principal factor determining the extractability of the anion appears to be the stoichiometry of the electrically neutral ion-pair $(R_2NH_2^+)_nMCl_x^{n-}$ that is formed, although other factors such as ionic size and polarizability are also important. Therefore, the packing of the required number of alkylammonium cations around the complex anion becomes more difficult as the charge on the latter is increased, the observed order of extractability[223] being, $MCl_4^- > MCl_4^{2-} \approx MCl_6^{2-} > MCl_6^{3-}$. The order also reflects the readiness with which the anions break away from the solvation interactions of the aqueous phase. Indeed, the tetrachloroaurate(III) anion, which is the only commonly occurring MCl_4^- species among this group of metals, is strongly extracted even by weakly basic reagents such as dibutyl carbitol (DBC; 6-ethoxydecan-5-ol),[232] methyl isobutyl ketone[223] and isodecanol.[233]

For dibutyl carbitol, spectrophotometric and other data[234] have been interpreted in terms of the formation of species such as $[H^+(H_2O)_4(DBC)_n]AuCl_4^-$. Since the PGM themselves are not extracted to any significant extent by these extractants, useful separations of gold from other precious metals can be made readily.

The extraction of gold from PGM solutions by dibutyl carbitol is used by Inco,[226] whereas extraction by methyl isobutyl ketone is used by Matthey Rustenburg Refiners.[224] In both instances, the extraction of the gold immediately precedes the respective extraction steps for palladium described previously. Base-metal anions, such as $FeCl_4^-$, which are extracted at high concentrations of aqueous chloride, can be removed by contacting the loaded organic phase with water or dilute hydrochloric acid. Under these conditions, the base-metal chloro anions are converted to the aquated cations, *e.g.*

$$FeCl_4^- + 6H_2O \longrightarrow Fe(H_2O)_6^{3+} + 4Cl^- \quad (82)$$

whereas the more stable $AuCl_4^-$ species ($\log\beta_4 \approx 26$) remains unaffected. Metallic gold of high purity can be recovered directly from the organic phase by the addition of solutions of oxalic acid, iron(II) or other reducing agents.[224,226] The process employing isodecanol as the extractant is more flexible, however, in that gold can be stripped from loaded organic phases by contact with water at 50 °C, enabling strip solutions containing up to 50 g of gold per litre to be obtained.[233]

The extraction of the PGM by amine salts was first reported some 30 years ago,[235] shortly after which a process for the recovery of the PGM by solvent extraction was patented in the Soviet Union.[236] The results of pilot-plant operations for the recovery of PGM from copper and nickel refinery slimes have also been described,[237,238] and it is probable that such processes are currently in full-scale commercial use. Further extensive studies by Soviet workers have been described in a recent review.[239] It has been shown that, in addition to the anion-exchange mechanism, *e.g.*

$$\overline{2RNH_3^+Cl^-} + PtCl_6^{2-} \longrightarrow \overline{(RNH_3^+)PtCl_6^-} + 2Cl^- \quad (83)$$

extraction can proceed *via* the irreversible formation of inner-sphere amine complexes, *e.g.*

$$\overline{2RNH_3^+Cl^-} + PtCl_6^{2-} \longrightarrow \overline{Pt(RNH_2)_2Cl_4} + 2Cl^- + 2HCl \quad (84)$$

The formation of inner-sphere complexes is favoured at relatively high pH values, and increases according to the type of amine in the order tertiary < secondary < primary, *i.e.* in the order of decreasing steric hindrance of the ligand.

In the solvent-extraction process of Matthey Rustenburg Refiners, the tertiary amine Alamine 336 (R_3N, where R = C_8–C_{10} alkyl groups) is used to extract platinum as $PtCl_6^{2-}$, after the extraction of palladium as described previously. So that a high selectivity can be achieved over iridium, the solution is first treated with a reducing agent to convert $IrCl_6^{2-}$ to $IrCl_6^{3-}$, the latter species being only very weakly extracted owing to its high ionic charge. Although the use of the tertiary amine minimizes problems associated with the progressive poisoning of the extractant caused by the formation of inner-sphere complexes, the extraction equilibrium (equation 83) lies so far to the right that the platinum cannot be stripped from the organic phase even by contact with highly concentrated chloride solutions (*e.g.* 10–12 M). The recovery of platinum from the organic phase is therefore accomplished by a deprotonation stripping process using sodium car-

bonate solution:

$$\overline{(R_3NH^+)_2PtCl_6^{2-}} + Na_2CO_3 \longrightarrow \overline{2R_3N} + PtCl_6^{2-} + 2Na^+ + H_2O + CO_2 \quad (85)$$

The free amine that is produced in this way must be reconverted to the chloride salt before recycle to the extraction stage. Moreover, the formation of hydrolysis products of the base-metal impurities present can result in the formation of solids at the aqueous–organic interface with a consequent deterioration in the phase-separation characteristics of the system.[224] Considerable effort has therefore been directed towards modification of the properties of tertiary or secondary amine extractants so that stripping with acid solutions (*e.g.* 6 M HCl) can be achieved. The incorporation of oxygen-containing additives, such as alcohols, phenols or carboxylic acids, into the organic phase, which was the subject of earlier Russian studies,[240] has been found useful in this respect and was recently patented.[241,242] For example, the addition of 50% (v/v) 2-ethylhexanoic acid to 0.25 M tris(tridecyl)amine in an aromatic solvent causes a sufficient decrease in the distribution coefficient for platinum to permit stripping with hydrochloric acid solutions of concentration higher than 3.0 M, while retaining sufficient extraction capacity for the efficient recovery of the metal at acid concentrations below 3.0 M. Such a decrease in the distribution coefficient probably occurs as a result of the solvating reactions between the amine salt and the additive, and effectively lowers the concentration of available extractant.

A different approach has been adopted in a process developed for use in South African refineries.[222,243] In this process, in which platinum and palladium are coextracted by anion-exchange extraction, it was found that the secondary amine Amberlite LA-2 suffered from extensive poisoning due to the irreversible formation of inner-sphere ammine complexes, especially those of palladium such as $Pd(R_2NH)_2Cl_2$. A modified extractant of the type $R_2NCH_2CO_2H$ was prepared from the parent amine, and was found to show no evidence of the formation of inner-sphere complexes. Moreover, the stripping of platinum and palladium from this reagent can be achieved readily with acid solutions, in spite of its tertiary amine structure. Although the reason for the relative ease of stripping is not clearly understood, it may be related to the occurrence of solvating interactions similar to those that occur when carboxylic acids are added to amine salts, as described previously.

In the Inco solvent extraction process,[226] platinum is extracted into tri-*n*-butyl phosphate (TBP), following the reduction of any iridium(IV) present to iridium(III) by sulfur dioxide. The extraction of the PGM by TBP has been reported to decrease through the series[244–246] $Pt^{IV} \approx Ir^{IV} > Pd^{IV} > Pd^{II} \approx Pt^{II} \gg Rh^{III} \approx Ir^{III}$. The extraction of species such as H_2IrCl_6 was suggested[244] without the extraction mechanism being considered, and the distribution data were recently discussed in terms of the generalized species $[H^+(H_2O)_a(TBP)_b]_m[MCl_x^{n-}]$, in which the extractant is assigned the role of solvating the hydrated proton.[246] It has been reported that the number of solvating TBP molecules depends upon the identity of the solvent used to dilute the extractant phase.[245] The extraction of platinum is carried out commercially under strongly acidic conditions (5–6 M HCl). Although the distribution coefficient for the extraction of platinum into TBP is not very high (typically 5), reasonably efficent recovery of the metal can be obtained in a four-stage countercurrent process. The stripping of platinum is achieved by contacting the loaded organic phase with water, under which conditions the weakly basic extractant is readily deprotonated. Iridium(IV) can be separated from rhodium(III) by extraction into TBP, and this method is reported to be used at the Hanau refinery of Degussa,[227] as well as at one or more of the South African PGM refineries. Amine salts also find commercial application in the extraction of iridium(IV) in the presence of rhodium(III) and base metals, stripping being achieved in this case by contacting the loaded organic phase with a solution of a reducing agent such as sodium hydrogen sulfite to reduce the metal complex to the weakly extracted $IrCl_6^{3-}$ species.[223,224]

Ruthenium and osmium are traditionally removed from solutions containing other PGM by distillation of their volatile tetroxides under oxidizing conditions. Osmium can be efficiently removed in this way even under quite strongly acidic conditions, and it would appear that little can be gained by the application of solvent-extraction technology to the recovery of this metal. For ruthenium, however, the oxidation process is more difficult, and the pH value of the solution must be maintained at a relatively high value, since the complete removal of RuO_4 is difficult to attain. The extraction of the molecular species by carbon tetrachloride has therefore been suggested as an alternative,[247] as has the extraction of the ruthenium(II) nitrosyl complex $[Ru(NO)Cl_5]^{2-}$ by amine salts,[248] the latter method having been used on a commercial scale in South Africa.[249]

Although rhodium has probably not been recovered commercially by solvent extraction, it can be extracted by quaternary ammonium salts under certain conditions,[250] the anion $[Rh_2Cl_9]^{3-}$ having been identified in extracts from aqueous phases containing the species $[Rh(H_2O)Cl_5]^{2-}$.

63.3.2.6 Solvent extraction of base metals by solvating extractants

The use of solvating extractants in the recovery of gold and platinum-group metals (PGM) was described in the previous section. These extractants have also found some specialized applications in the extractive metallurgy of base metals. For example, they have been used in the recovery of uranium, the separation of zirconium and hafnium, the separation of niobium and tantalum, the removal of iron from solutions of cobalt and nickel chlorides, and in the separation of the rare-earth metals from one another.

Although solvating extractants such as TBP are still widely employed in the purification of uranium for nuclear purposes and in the reprocessing of spent nuclear fuels (neither of which applications lies within the scope of this review), their use in the extractive metallurgy of uranium is largely only of historical significance. In the USA during the period 1942 to 1953, solutions obtained by the dissolution of rich pitchblende ores in nitric acid were extracted with diethyl ether, the process owing its origins to the early observations of Peligot.[251] The first cycle of extraction was carried out on an aqueous feed solution containing 200 g of uranium per litre and 1 M free nitric acid. The loaded organic phase was stripped with water, and the strip liquor was evaporated to a uranium content of 1000 g l^{-1}. This removed excess nitric acid and destroyed any coextracted heteropoly acids of molybdenum and vanadium. The strip liquor was treated in a second extraction cycle at low acidity to give a uranyl product of high purity.[252,253]

Uranyl nitrate has been extracted into solvents such as diethyl ether as the entity $[UO_2(NO_3)_2(H_2O)_4]$ solvated by two to six molecules of the organic solvent.[254–256] The solvation is usually considered to be of the secondary type, in which the solvent molecules are attached by hydrogen bonding to the water molecules in the primary hydration shell. However, IR data have been presented[257,258] to support Muller's earlier hypothesis[259] that only two of the water molecules are directly bound to the uranyl cation, the remaining coordination sites being occupied by solvent molecules.

So that the much stronger extraction of uranyl nitrate compared with the nitrates of the transition metals (*e.g.* the partition coefficients for Mn^{2+}, Co^{2+}, Cu^{2+} and UO_2^{2+} lie in the ratio 0.1:1.0:2.0:10^7) can be rationalized, it has been suggested that the water and nitrate in the extracted species are both covalently bonded to UO_2^{2+} by hybrid orbitals involving electrons of the *f*-shell.[254] The direct contact of the metal and the nitrate has been confirmed by IR spectroscopy.[258] Solid compounds of the types $UO_2(NO_3)_2 \cdot 3H_2O \cdot S$ and $UO_2(NO_3)_2 \cdot 2H_2O \cdot 2S$ (where S represents the organic solvent molecule), in which the metal ion retains a coordination number of eight, have been isolated from organic extracts of uranyl nitrate.[260]

The commercial extraction of uranium by diethyl ether was replaced in the early 1950s by a single-cycle process using TBP (20–30% in kerosene or hexane).[252] The feed solution was treated with phosphate to form a complex with thorium(IV), and with aluminum(III) to form a complex with fluoride ions, and adjusted to 200–400 g of uranium per litre and 1–3 M free nitric acid. Uranium was stripped from the loaded organic phase into water at 65 °C to give a strip liquor containing 100 g of uranium per litre and less than 0.1 M free nitric acid. In the UKAEA process, uranium was precipitated as ammonium diuranate, calcined to UO_3 or U_3O_8, and reduced with hydrogen to UO_2. In the USAEC process, uranyl nitrate was converted by 'thermal denitration' to UO_3, which was subsequently reduced with hydrogen to UO_2. It is reported that TBP still finds use in the primary extraction of uranium on plants at Palabora (South Africa),[261] Forez (France)[262] and Mounana (Gabon).[262] At the Palabora plant, a uranothorianite concentrate is leached in hot nitric acid to produce a liquor containing 25–35 g of uranium and 105–125 g of thorium per litre. Uranium, together with some thorium, is extracted into a 10% solution of TBP in kerosene. The coextracted thorium, which is rather less strongly extracted than uranium,[263] is displaced from the organic phase by being contacted with a concentrated solution of uranyl nitrate, after which the uranium is stripped from the organic phase by water at 40–50 °C. The strip liquor is subsequently treated with ammonia gas to precipitate an ammonium diuranate product containing less than 0.6% thorium.

It is generally agreed that the extracted uranium species is $UO_2(NO_3)_2(TBP)_2$[127,264,265] in which, in contrast to the species extracted into ether, the extractant molecules are directly coordinated to the metal ion. The extraction of uranium(VI) by neutral organophosphorus compounds increases with the number of C—P bonds (as opposed to C—O—P bonds) and with the increased branching of the substituent alkyl groups, as would be expected from the effect of these changes on the electron-donor properties of the phosphoryl group. The extracted thorium(IV) complex has been formulated as $Th(NO_3)_4 \cdot 2S$[266,267] and as $Th(NO_3)_4 \cdot 3S$,[268,269] and its composition may depend to some extent on the conditions of extraction. The extraction of thorium (like that of

uranium(VI)) is also enhanced by the replacement of C—O—P bonds in the extractant with C—P linkages, but the extraction of thorium (unlike that of uranium) is depressed when branched alkyl groups are introduced into the extractant molecule. This result has been explained in terms of the increased importance of steric effects in the $Th(NO_3)_4 \cdot 3S$ complex as compared with those in $UO_2(NO_3)_2 \cdot 2S$.[270]

Processes have been developed[271] for the recovery of thorium by solvent extraction into solutions of TBP, but their present status is uncertain owing to the limited market for this metal (although some countries are reportedly stockpiling thorium for future use in nuclear applications).

The solvent extraction of rare-earth nitrates into solutions of TBP has been used commercially for the production of high-purity oxides of yttrium, lanthanum, praseodymium and neodymium from various mineral concentrates,[39] as well as for the recovery of mixed rare-earth oxides as a byproduct in the manufacture of phosphoric acid from apatite ores.[272,273] In both instances, extraction is carried out from concentrated nitrate solutions, and the loaded organic phases are stripped with water. The rare-earth metals are precipitated from the strip liquors in the form of hydroxides or oxalates, both of which can be calcined to the oxides. Since the distribution coefficients (D) for adjacent rare earths are closely similar, mixer–settler assemblies with 50 or more stages operated under conditions of total reflux are necessary to yield products of adequate purity.[39]

Initial fundamental studies[274,275] prompted the suggestion that the extractability of the lanthanides by TBP increased regularly through the series, with a linear dependence of $\log D$ upon atomic number. However, subsequent work[276,277] revealed that the linear dependence was not observed over the entire series, and that discontinuities in slope, or maxima, were always obtained in the region from europium to dysprosium. The changes in the entropy and enthalpy of the extraction reaction also vary in a discontinuous manner, while the changes in the free energy show evidence of a tetrad effect.[278] Furthermore, the initial proposal[276] that the extracted complexes were hydrated species of the type $[M(TBP)_a(H_2O)_{x-a}](NO_3)_3$, where x is probably 6, was later rejected in favour of the formation of anhydrous trisolvates $M(NO_3)_3 \cdot 3TBP$, at low[279] as well as high concentrations[280] of metal in the organic phase. In view of the existence of water-saturated TBP as the monohydrate $TBP \cdot H_2O$, the extraction of the lanthanides can be formulated as

$$M^{3+} + 3NO_3^- + \overline{3TBP \cdot H_2O} \longrightarrow \overline{M(NO_3)_3 \cdot 3TBP} + 3H_2O \qquad (86)$$

It has been confirmed that the water content of the organic phase varies inversely with the concentration of extracted metal, and falls to zero for metal-saturated solutions.[281]

The discontinuous variation in the extractability of the lanthanides with atomic number has been interpreted as signifying a change in the coordination number of the metal ions in the extracted complex across the series.[282] Therefore, from a study of the electronic spectra of the extracted complexes of neodymium and erbium, it was concluded that the metal ions are eight- and six-coordinate respectively. The difference in coordination was proposed to result from the existence of two bidentate nitrate ligands and one monodentate nitrate ligand in $Nd(NO_3)_3 \cdot 3TBP$, whereas all three nitrate ligands in $Er(NO_3)_3 \cdot 3TBP$ are monodentate.[282] NMR studies of the proton and ^{31}P chemical shifts for the lanthanide complexes of tri-*n*-pentyl phosphate also showed a difference between the structures of the complexes of the light and heavy lanthanides.[283] However, a more recent study of the lanthanide-induced chemical shifts of the α-CH_2 protons in the TBP complexes provided no evidence for a change in coordination across the series, although the remoteness of these protons from the metal coordination centre may preclude their sensitivity to such changes.[284]

A review of the solvent extraction of the rare-earth metals has been published.[111]

Solvent extraction has proved to be the most effective method for the separation of zirconium and hafnium, which invariably occur in nature in close association, owing to their almost identical chemical properties. These metals have found considerable use in the nuclear-power industry on account of their unusually high (hafnium) and low (zirconium) neutron-capture cross-sections. It is evident that the mutual separation of the two metals must be of a high degree to make them suitable for such applications. Two different solvent-extraction processes are known to be used on a commercial scale; in one process, zirconium is selectively extracted from nitrate media into TBP; in the second process, hafnium is selectively extracted from thiocyanate solutions into methyl isobutyl ketone (MIBK).

In the TBP process, which was developed in the USA[285] and in England,[286] zirconium(IV) hydroxide (produced, for example, by the hydrolysis of the material obtained from the caustic fusion of zircon sand) is dissolved in nitric acid to give a solution containing 30–100 g of zirconium (plus hafnium) per litre and 5–8 M free nitric acid. The zirconium is extracted into a 50–60% solution of TBP in a suitable hydrocarbon diluent, the loaded organic phase is washed in 5 M nitric

acid to remove coextracted hafnium, and the zirconium is stripped into water to produce a pure solution of the nitrate. The process has been described in detail in several publications.[285–290]

Fundamental studies of the distribution of zirconium(IV) between dilute solutions of TBP in kerosene and aqueous nitric acid indicate that the disolvate $Zr(NO_3)_4 \cdot 2TBP$ is present in the organic phase,[291,292] although the presence of the monosolvate $Zr(NO_3)_4 \cdot TBP$ at low concentrations of extractant has also been suggested.[293,294] Hafnium has been shown to behave in an analogous manner.[294] The second-order dependence of metal distribution upon the concentration of hydrogen ion in the aqueous phase has been interpreted in terms of the extraction reaction

$$MO^{2+} + 2H^+ + 4NO_3^- + \overline{2TBP} \longrightarrow \overline{M(NO_3)_4 \cdot 2TBP} + H_2O \quad (87)$$

However, in a recent study,[295] distribution data were adequately represented in terms of the reactions (88) and (89).

$$Zr^{4+} + 4NO_3^- + \overline{2TBP} \longrightarrow \overline{Zr(NO_3)_4 \cdot 2TBP} \quad (88)$$

$$ZrOH^{3+} + 3NO_3^- + \overline{2TBP} \longrightarrow \overline{Zr(OH)(NO_3)_3 \cdot 2TBP} \quad (89)$$

Inextractable $Zr_3(OH)_4^{8+}$ and other polymeric species were considered to be present in the aqueous phase.[295]

The selectivity of neutral organophosphorus compounds for the extraction of zirconium over hafnium in nitrate media appears to result from the combination of a number of factors. The stability constants of the nitrate complexes of zirconium are slightly higher than those of the corresponding hafnium complexes.[296] Furthermore, the difference between the P=O stretching frequencies in the free extractant and the metal complex is greater for zirconium (60 cm^{-1}) than for hafnium (45 cm^{-1}), indicating the greater strength of the solvating interaction for the former metal.[297] Differences for the two metals in the extent of formation of hydrolyzed[298] and polymerized species[299] in the aqueous phase are also undoubtedly important.

The selective extraction of hafnium from thiocyanate media into diethyl ether was first reported in 1947.[300,301] The technique was subsequently investigated extensively in the USA with a view to the development of a suitable industrial-scale process, it being found advantageous for MIBK to be used as the solvent in place of diethyl ether.[302] The first commercial plant was completed in 1952,[303] and the process has since been used widely in the USA, England, France, Germany and Japan. Several descriptions of the process have been given in the literature.[287–289,303–305]

In a typical operation, a solution of zirconium and hafnium chlorides (1.3 M total metal with a hafnium content of 2–3% by mass) containing 1 M hydrochloric acid and 3 M ammonium thiocyanate is extracted in column contactors with a solution of thiocyanic acid (0.5 M) in MIBK, to produce a raffinate containing about 50 mg of hafnium per litre. The loaded organic phase is scrubbed with 3.5 M hydrochloric acid to remove coextracted zirconium (the resulting aqueous phase being recycled to the extraction circuit), and the hafnium is subsequently stripped from the organic phase with 2.5 M sulfuric acid to give a solution of hafnium(IV) sulfate containing about 2% zirconium.

The reasons for the selective extraction of hafnium over zirconium from thiocyanate solutions by solvating extractants are not well understood. Hence, a recent review of the chemistry of these metals described the separation process but offered no explanation for the observed selectivity.[306] There is no evidence that differences in the stabilities of the thiocyanate complexes of hafnium(IV) and zirconium(IV) are responsible for the selective extraction of the former, since the formation constants of the respective complexes are essentially identical for both metals.[307] However, there is some indication that the hafnium thiocyanates are more readily solvated by the extractant than are the corresponding complexes of zirconium.

For tri-*n*-octylphosphine oxide, for example, the shift in the P=O stretching frequency from its value for the free extractant is greater for the hafnium complex (85 cm^{-1}) than for the zirconium complex (70 cm^{-1}).[297]

Several studies have been carried out in attempts to determine the stoichiometry of the extracted complexes, and it is generally agreed that hydroxo complexes of the type $[Zr(OH)_x(NCS)_{4-x}]$ solvated by one or two molecules of extractant are the predominant species in the organic phase.[308–314]

Most frequently, the number of thiocyanate moieties in the extracted complex is equal to two, although some authors consider that the extracted species changes progressively to the trithiocyanato complex ($x = 1$) and tetrathiocyanato complex ($x = 0$) on the successive extraction of a given aqueous phase.[312] IR data show that the thiocyanate groups are bound to the metal *via* the nitrogen atom,[315] as would be expected from the distinct A-character of zirconium(IV).

In a recent study in which MIBK was used as the extractant,[316] the distribution data were found to be consistent with the reaction

$$ZrO^{2+} + 2NCS^- + \overline{2MIBK} \longrightarrow \overline{ZrO(NCS)_2 \cdot 2MIBK} \quad (90)$$

although, in the view of the doubtful integrity of the ZrO^{2+} ion, the extracted complex could equally well be formulated as $Zr(OH)_2(NCS)_2 \cdot 2MIBK$. Furthermore, it has been concluded from IR studies of the complexes of hafnium(IV) extracted from thiocyanate solutions by cyclohexanone that no metal–oxygen double bonds are present.[314]

As was observed in the case of the extraction of zirconium and hafnium from nitrate media, it is probable that the different tendencies of the metals towards hydrolysis has some effect on the selectivity observed,[298,313] expecially in view of the proved extraction of hydroxo complexes. The extraction of both metals decreases markedly in the presence of sulfate ions in the aqueous phase (a feature that is utilized in the stripping of the loaded hafnium with sulfuric acid), although the selectivity for hafnium over zirconium is simultaneously increased on account of the higher stability constants of the inextractable sulfato complexes of zirconium.[298]

The separation of niobium and tantalum by solvent extraction has been carried out on a commercial scale for about 30 years, and has totally superseded the previously used Marignac process based on the fractional crystallization of K_2TaF_7 and $K_2NbOF_5 \cdot H_2O$ from dilute hydrofluoric acid.[317,318]

Early work showed that tantalum could be separated from niobium by being extracted from mixtures of hydrofluoric and mineral acids into diisopropyl ketone.[319] Niobium was also found to be extracted at higher acidities and high concentrations of hydrofluoric acid.[320] Subsequently, a solvent-extraction process using methyl isobutyl ketone (MIBK) was developed at the US Bureau of Mines Laboratories in Albany, Oregon, and was put into commercial operation by the Wah Chang Corp. in Albany in 1956.[321] In that process, columbite and tantalite ores are dissolved in 70% hydrofluoric acid, and the resulting solution, containing 10–15 M free hydrofluoric acid, is contacted with MIBK in the presence of sulfuric acid in polyethylene pulsed-plate columns. The coextracted niobium and tantalum are separated in a second column by the stripping of the niobium into dilute acid, and the tantalum is subsequently stripped from the organic phase by being contacted with a large volume of water. Niobium(V) and tantalum(V) oxides are precipitated from the respective strip liquors with ammonia. An essentially similar process is used by Fansteel Metallurgical Corp. at Muskogee, Oklahoma.[322] There, however, contactors of the mixer–settler type are used in the solvent-extraction operation, and tantalum is recovered from the strip liquor by the addition of potassium fluoride solution to precipitate K_2TaF_7, which is used for the recovery of tantalum metal by fused-salt electrolysis.

The use of TBP in place of ketone extractants has also been reported;[323] this reagent offers the advantages of higher separation factors and lower losses of extractant to the aqueous phase.[324,325]

The preferential extraction of tantalum over niobium from weakly acidic fluoride solutions appears to result from the predominance of inextractable hydrolyzed niobium species such as H_2NbOF_5 under these conditions; tantalum, in contrast, is present largely in the form of extractable $HTaF_6$ and H_2TaF_7. At high concentrations of hydrofluoric acid, the extraction of niobium is enhanced owing to the formation of significant amounts of $HNbF_6$. The increased extraction of niobium in the presence of mineral acids can be related to the suppression of the hydrolysis reaction

$$HNbF_6 + H_2O \longrightarrow H_2NbOF_5 + HF \quad (91)$$

Distribution data suggest that when TBP is used the extracted niobium compound is associated with three molecules of extractant, whereas the tantalum compound is associated with two molecules of extractant except at very low metal loadings.[326] Nevertheless, it is likely that the role of the extractant is to solvate the proton component of the extracted fluorometallic acid rather than to solvate the metal ion directly.

Commercial applications of solvating extractants in the extractive metallurgy of the more-common base metals are very limited in number, the only well-known example being the use of TBP for the removal of iron from solutions of cobalt and nickel chlorides.[191] Nevertheless, it is probable that the use of solvating extractants (particularly neutral organophosphorus compounds) will become more widespread with the increasing acceptance of chloride-based routes for the processing of certain base-metal ores, especially complex sulfides of zinc[327,328] and copper.[329,330]

At the Falconbridge Nikkelverk in Norway, iron(III) is extracted from a solution of 4.5 M hydrochloric acid containing nickel (120 g l^{-1}) and iron, copper and cobalt (2 g l^{-1} each). The organic phase consists of a 4% solution of TBP in an aromatic solvent, and two stages of extraction suffice to reduce the iron content of the aqueous phase to 0.005 g l^{-1}. The loaded organic phase

is stripped with water in three stages to give a solution containing 33 g of iron per litre in 0.7 M hydrochloric acid.[191]

It was concluded from a superficial study of the dependence of the distribution of iron(III) on the concentration of TBP in chloroform that a complex of stoichiometry $FeCl_3 \cdot 3TBP$ was extracted from 2 M hydrochloric acid, whereas a complex of stoichiometry $H[FeCl_4(TBP)_2]$ was extracted from 6 M hydrochloric acid.[331] The coordination of iron(III) was assumed to be octahedral in both instances. A similar conclusion was reached for solutions of TBP in benzene, the regions of extraction of the different complexes being given as 4 M and 7–9 M hydrochloric acid respectively.[332] However, it was subsequently shown that in all instances the electronic spectra of the extracts are those of the tetrahedral $FeCl_4^-$ species,[333] and that the mechanism of extraction is therefore apparently analogous to that for the extraction of iron(III) from chloride solutions by reagents such as ethers, ketones and esters where the extracted complex is of the type $[H^+ \cdot nS \cdot mH_2O][FeCl_4^-]$. It has been shown that the electronic,[334,335] IR,[336,339] and proton magnetic resonance spectra[340] of such complexes are consistent with the solvation of the proton rather than the metal ion by the extractant, the metal ion remaining in the form of the tetrahedral $FeCl_4^-$ species with no primary solvation or hydration. Water also plays an important role in the formation of the extractable complex, anhydrous $HFeCl_4 \cdot 2S$ (where S = diisopropyl ether), for example, becoming soluble in excess ether only after the addition of 5 mol of water per mol of complex and the formation of the species $[H_3O^+ \cdot 4H_2O \cdot nS][FeCl_4^-]$.[335]

63.3.3 Ion-exchange Processes

As early as the middle of the nineteenth century it was observed that certain naturally occurring substances could extract and concentrate ions from their environment.[341,342] However, 50 years elapsed before ion exchange, as the process became known, was used on an industrial scale for water-softening,[343] and another 50 years before ion exchange came of age as a metallurgical process with the advent of the atomic age and the worldwide demand for uranium that accompanied it.

The term ion exchange, as used by extractive metallurgists, refers to processes in which a solution containing a mixture of metal ions is contacted with a resin that is insoluble in the metal ion solution. A modern ion-exchange resin consists of a chemically inert organic matrix to which labile functional groups are chemically bonded. These groups interact with and extract metal ions from aqueous solutions. The reaction is generally reversible so that, by alteration of the chemical environment, the metal ions can be subsequently reextracted back into the solution phase. The twin objectives in this operation are always the production of a more concentrated metal solution and the separation of the desired metal ion from other species that may be present in the original solution.

The early development of ion exchange as a unit operation in hydrometallurgy was slow, mainly because of the lack of selectivity of the resins under operating conditions, and the limited capacities of the earlier commercial resins. Consequently, ion exchange found applications only in processes where the concentration of metal ions in solution was very low, and where the resin could be used to upgrade the solution prior to some final purification step. Recent developments, however, particularly the introduction of chelating resins, have considerably broadened the scope of resins in hydrometallurgy.

Ion-exchange resins have developed from naturally occurring aluminosilicates[341,342] to synthetic silicates, and finally (as a result of the discovery in 1935[344] that polar groups could be fixed to a polymeric matrix) to organic ion-exchange resins. The inert organic backbone in such resins usually consists of polystyrene crosslinked with divinylbenzene, while the functional group bonded to the backbone generally falls into one of three groups, *viz.* anionic, cationic or chelating. The chemistry involved in the interactions between these various functional groups and metal ions in solution is generally the same in ion exchange as in solvent extraction; therefore, for a range of metal ions, the order of selectivity and the relative distribution between the solution and the extractant are also similar. As a broad generalization it can be stated that ion exchange would probably only be preferred to solvent extraction in the hydrometallurgical processing of low-grade solutions. In these situations solvent losses in solvent extraction become relatively important, whereas the polymeric ion-exchange resins are effectively insoluble in water and do not suffer from this drawback. However, perhaps the greatest advantage of resins is their ability to treat metal solutions containing appreciable quantities of suspended solids, since this eliminates the necessity for the costly solution-clarification steps that are indispensable in solvent-extraction processes.

Resins with cation-exchange functionality are available either as strongly or weakly acidic ion exchangers. The strong-acid resins have sulfonic acid ($—SO_3H$) functional groups, whereas the

weak-acid resins have carboxylic acid (—CO_2H) functional groups. The mechanism of extraction is by the exchange of hydrated metal cations in solution with hydrogen ions on the functional groups, the pH value of the aqueous solution being the most important factor in the determination of metal extractability, particularly for the weak-acid resins. The metal ions remain in the outer Helmholtz layer in the hydrated state, and electrostatic interaction without dehydration accounts for the reversibility of absorption. Cation-exchange resins are not particularly selective, but some separation of the metals can be achieved on the basis of their ionic charge and size.[345]

Two types of anion-exchange resins are available: strong- and weak-base resins. The resins with strong-base functionality have quaternary amine functional groups, whereas the active groups on weak-base resins are primary, secondary or tertiary amines, or a mixture of the three. The mechanism of extraction is by the exchange of complexed metal anions in solution with simple inorganic anions, such as chloride, nitrate, sulfate, or bisulfate, which are associated with the amine in the resin phase. Anion-exchange resins have better selectivity than cation-exchange resins, owing to the ability of certain metals to form anionic complexes in solution, whereas other metals in the same solution do not.[346–348]

In anion and cation exchange, the metal ion is generally held in the resin phase by coulombic forces, although in some instances (the extraction of copper by weak-acid resins, for example) there is evidence of complex formation. Strong-acid and strong-base resins are completely ionized in aqueous solutions in the pH range 2–12, and exhibit maximum ion-exchange capacity under these conditions. Weak-acid and weak-base resins are ionized only at pH values higher than 5 (for —CO_2H) and lower than 9 (for —NR_2). Their capacities tend to be lower than those of the strong-acid and strong-base resins, but they often exhibit better selectivities for metals.

The chelating resins are generally acidic, and the metal cations are extracted by exchange with protons on the functional groups of the resin. The reactions are therefore of the cation-exchange type but, in contrast to simple cation exchange, the metal cation coordinates with the functional group of the resin, forming strong covalent bonds. The chelating resins are therefore more specific for certain metals than the cation-exchange resins, which allows greater selectivity. Some examples of the functional groups in chelating resins are the iminodiacetate, iminophosphonate, picolylamine and pyridylimidazole groups.

The use of ion-exchange resins in extractive metallurgy will be discussed in terms of these three basic types of resins and the chemistry of metal complexation in aqueous solutions, with particular reference to current applications in the hydrometallurgical industry. While the electrostatic interactions in anion- and cation-exchange resins are not strictly within the domain of coordination chemistry, the extractability of metal ions is nonetheless significantly influenced by the extent of their reaction with their aqueous environment. For example, the capacity and selectivity of cation-exchange resins for metal cations depends largely on the degree of coordination of water molecules to the metal ion, whereas the metal-extraction properties of anion-exchange resins depend on the extent of coordination between metal cations and anionic ligands in solution.

63.3.3.1 Cation-exchange resins

(i) Principles

Cation-exchange resins extract metal ions from aqueous solutions by forming the metal salt of the acidic functional groups on the resin. This type of reaction can be represented by the following simple equation

$$M(H_2O)_x^{n+} + n|\text{—RH} \rightleftharpoons (|\text{—R})_nM(H_2O)_x + nH^+ \tag{92}$$

where R represents the organic acid anion and the symbol |— represents the inert polymeric matrix. The equilibrium in equation (92) is usually defined as a mass-distribution ratio such as

$$D = \frac{\text{metal ion (mol)/dry resin (g)}}{\text{metal ion (mol)/solution (ml)}} \tag{93}$$

and the equilibrium value is determined by the pK_a of the functional groups (*i.e.* the pH value at which 50% of the groups are ionized) and by the strength of the interaction between the metal cation and the organic acid. The ion-exchange behaviour of cation-exchange resin is determined predominantly by the functional groups; the number of fixed ionic groups determines the resin capacity, while the acid strength of the groups determines the effective operating pH range of the resin. Elution of the metals from the resin is achieved by shifting of the equilibrium in equation (92) to the left through mass action, *i.e.* by an increase in the concentration of hydrogen ions or of some other competing cationic species. Weak-acid resins can be eluted with essentially a stoi-

chiometric amount of acid, whereas strong-acid resins require a substantial excess of acid or of some other cation.

The predominant influence that determines the selectivity of a cation-exchange resin is the strength of the ion-pair that is formed between the hydrated metal cation and the ionized acidic functional group. As the bond formed is essentially electrostatic in nature, the selectivity is determined by the ionic charge on the metal cation and the distance of closest approach to the functional group, *i.e.* by the size of the hydrated metal ion. Since the degree of hydration of metal cations decreases with increasing atomic number, the selectivity, as a general rule, increases with increasing valence and atomic number. This is illustrated by the results in Table 3, which show the affinities of the Duolite strong-acid resin for various monovalent and divalent cations (at concentrations in the range 0.01 to 0.1 M) relative to the hydrogen ion. The striking feature of these results is the poor selectivity of the cation-exchange resins; in particular, separations within a group of metals (*e.g.* the first transition series: iron, zinc, copper, cobalt, nickel) are so small as to be of no practical value. The other interesting feature of these results is the role of the matrix in determining the selectivity of the resin. Divinylbenzene (DVB) is introduced as a crosslinking agent in polystyrene resins, an increase in crosslinking leading to an increase in the mechanical strength of the resin. However, an increase in DVB also leads to a decrease in the extent to which the resin will swell in solution and, consequently, to a decrease in the average pore size. The resin therefore becomes more selective for smaller cations with increasing DVB, and this effect is also illustrated in Table 3.

Table 3 Relative Affinities of Various Ions for the Strong-acid Resin Duolite C-20[a]

	4% DVB	*8% DVB*	*12% DVB*	*16% DVB*
Monovalent cations				
H	1.0	1.0	1.0	1.0
Li	0.90	0.85	0.81	0.74
Na	1.3	1.5	1.7	1.9
NH_4	1.6	1.95	2.3	2.5
K	1.75	2.5	3.05	3.35
Rb	1.9	2.6	3.1	3.4
Cs	2.0	2.7	3.2	3.45
Cu	3.2	5.3	9.5	14.5
Ag	6.0	7.6	12.0	17.0
Divalent cations				
Mn	2.2	2.35	2.5	2.7
Mg	2.4	2.5	2.6	2.8
Fe	2.4	2.55	2.7	2.9
Zn	2.6	2.7	2.8	3.0
Co	2.65	2.8	2.9	3.05
Cu	2.7	2.9	3.1	3.6
Cd	2.8	2.95	3.3	3.95
Ni	2.85	3.0	3.1	3.25
Ca	3.4	3.9	4.6	5.8
Sr	3.85	4.95	6.25	8.1
Hg	5.1	7.2	9.7	14.0
Pb	5.4	7.5	10.1	14.5
Ba	6.15	8.7	11.6	16.5

[a] From Warshawsky, ref. 348.

In considering the extraction of metal cations by strong-acid resins in the presence of competing hydrogen ions, some approximations can be made. Monovalent cations absorb below hydrogen ion concentrations of 0.5–1 M, divalent cations below 1–2 M, and trivalent cations below 2–3 M, while a tetravalent cation, such as the Th^{4+} ion, is strongly extracted at all acidities. In those instances where the ionic charge of the metal ion is less than the oxidation number (*e.g.* the uranyl ion UO_2^{2+} or the vanadyl ion VO^{2+}), the cation-exchange behaviour is determined by the ionic charge and not the valency of the metal.

Weak-acid resins generally extract metal ions only at a pH value of 3 or more. At high pH values, where the carboxylic acid functional group is predominantly ionized, the metal-extraction behaviour of a weak-acid resin parallels that of a strong-acid resin. The weak-acid resins tend to be more selective than strong-acid resins, however, and practical separations of metals are possible. In certain interactions between metal ions and weak-acid resins it is difficult to determine whether the interaction is purely electrostatic or whether chemical bonds are formed. In particular, there is strong evidence[349] that Ag^+ and Cu^{2+} form complexes with carboxylic acid groups. Copper, in

fact, has such an affinity for weak-acid resins that, in the pH range 4–5, it can be extracted quite selectively from a solution containing cobalt and nickel.

A secondary, more subtle, effect that can be utilized in the achievement of selectivity in cation exchange is the selective complexation of certain metal ions with anionic ligands. This reduces the net positive charge of those ions and decreases their extraction by the resin. In certain instances, where stable anionic complexes form, extraction is suppressed completely. This technique has been utilized in the separation of cobalt and nickel from iron, by masking of the iron as a neutral or anionic complex with citrate[350] or tartrate.[351] Similarly, a high chloride concentration would complex the cobalt and the iron as anionic complexes and allow nickel, which does not form anionic chloro complexes, to be extracted selectively by a cation-exchange resin.

(ii) Applications

Most of the applications of cation exchange in the recovery of metals from aqueous solutions are several decades old. Early attempts to employ cation exchange for the recovery of metals from primary sources failed because of the lack of selectivity. For example, the extraction of uranium from sulfuric acid leach liquors failed owing to the extensive coextraction of iron, aluminum and manganese. Over the years a number of studies have been carried out on the recovery of cobalt and nickel from the tailings of acid-leach hydrometallurgical operations. Because of their value and relatively low concentration in these solutions (100–1000 mg l^{-1}), they are ideal for recovery by ion exchange. The studies have shown that nickel and cobalt (also copper or zinc) present in solutions containing a large excess of sodium, potassium, calcium and magnesium can be selectively extracted with weak-acid resins. No large-scale commercial installations have been introduced, however, and the chelating resins would probably be preferred in this application nowadays. Cation-exchange resins have therefore found their widest application in the removal of heavy metals from industrial liquors, but the objective in these applications, because of the lack of selectivity, has generally been water purification rather than metal recovery.

One exception has been the treatment of the rare-earth elements. The separation of the rare earths by cation-exchange chromatography[352] was developed originally for analytical purposes, but the technique was extended to a commercial scale for the preparation of individual rare-earth metals in a very pure state. The method involves loading of all the rare-earth metals non-selectively from a chloride leach liquor onto a strong-acid resin, followed by selective elution with a 0.1% solution of citrate buffered at a value of pH 8. The citrate ion forms complexes most strongly with the heaviest metals, thus reducing their effective positive charge and enhancing their rate of elution relative to the lighter metals in the series. The rare-earth metals emerge from the resin column in the order Er > Ho > Dy > Tb > Gd > Eu, and individual rare earths with a purity greater than 99.9%[353] can be produced.

Another important industrial application of cation-exchange resins is in the regeneration of electroplating baths. Chromium has many applications in metal-finishing and aluminum-anodizing operations and, since it is highly toxic on the one hand and relatively valuable on the other, several ion-exchange processes have been developed for the regeneration of spent electroplating baths. Impurities such as iron, aluminum and manganese or valuable metals such as nickel,[354] copper or zinc[355] are removed from the solutions of chromic acid and sulfuric acid with a cation-exchange resin. The anionic chromic acid can be recycled to a plating bath or can be concentrated on an anion-exchange resin.[356]

Finally, one of the first continuous ion-exchange plants installed used a weak-acid resin to recover copper from rayon-fibre spinning solutions. In the Bemberg or copper(II) ammonium process,[357] the spinning takes place in an acidic copper sulfate solution, and the fibre is then washed in ammonia solution. The wash water contains as much as 30% of the copper required for the spinning operation and its recovery is important in economic and environmental terms. The copper is extracted as the cationic amine complex by the weak-acid resin, and is then stripped from the resin with the acidic spinning solution. Zinc is recovered in a similar manner from vicrose rayon-spinning operations.

63.3.3.2 Anion-exchange resins

(i) Principles

Strong- and weak-base resins exchange anions with their aqueous environment and therefore extract only metals that form anionic complexes in solution. Strong- and weak-base resins display a similar affinity for anionic species, which increases with the charge and the polarizability of the anion. Strong-base resins have quaternary amine functional groups that possess a permanent

positive charge and extract metal ions of general formula ML_x^{n-} (where L is an anionic ligand), according to the following equation:

$$ML_x^{n-} + n|{-}\overset{+}{N}R_3X^- \rightleftharpoons (|{-}\overset{+}{N}R_3)_nML_x^{n-} + nX^- \quad (94)$$

The equilibrium in equation (94) is generally defined as a mass-distribution ratio such as that shown above for cation-exchange resins (equation 93), and the position of the equilibrium is determined by the relative concentration of the counter-ion ML_x^{n-} and the co-ion X^-. The nature of the quaternary amine has little effect on the equilibrium properties of the resin, and the chemistry of metal complex formation in aqueous solution is the dominant factor.

Weak-base resins have primary, secondary or tertiary amine functional groups and, in neutral or alkaline solution, the amines are in the free-base (un-ionized) form and have no ion-exchange properties. In acidic solution, the amine groups are protonated and extract anions according to the following equations:

$$|{-}NR_2 + HX \rightleftharpoons |{-}\overset{+}{N}R_2HX^- \quad (95)$$

and

$$n|{-}\overset{+}{N}R_2HX^- + ML_x^{n-} \rightleftharpoons (|{-}\overset{+}{N}R_2H)_nML_x^{n-} + nX^- \quad (96)$$

The pK_a of the weak-base resins is determined by the basicity of the amine functional groups and by the nature of the anion in solution. Since the strength of the ion-pair increases with the charge and polarizability of the anion, the driving force for ion-pair formation permits proton uptake from far more alkaline solutions when strong ion-pairs are formed. For example, the strength of the ion-pair formed between the large polymeric amine cation of a weak-base resin and the large, very stable and highly polarizable anion $Au(CN)_2^-$ yields a pK_a of about 9–10,[358] whereas the pK_a of the same resin in chloride solution is some 2 log units lower.

Anion-exchange resins are eluted either by reversal of the equilibria shown in equations (94) to (96) or, in some cases, by chemical destruction of the anionic complex ML_x^{n-}. The elution of strong-base resins requires a large excess of the co-ion, X^-, whereas the elution of weak-base resins can be achieved most effectively by treatment of the resin with a stoichiometric amount of hydroxide ions, which restores the resin to the free-base form:

$$(|{-}\overset{+}{N}R_2H)_nML_x^{n-} + nOH^- \rightleftharpoons n|{-}NR_2 + ML_x^{n-} \quad (97)$$

An example of chemical destruction of an anionic species is the elution of aurocyanide from an anion-exchange resin with thiourea, a neutral ligand that reacts with gold cyanide in the presence of acid to form a cationic complex. The elution reaction can be described by the following equation:

$$|{-}\overset{+}{N}R_3Au(CN)_2^- + 2CS(NH_2)_2 + 2H_2SO_4 \longrightarrow 2HCN + |{-}\overset{+}{N}R_3HSO_4^- + [Au\{CS(NH_2)_2\}_2]^+HSO_4^- \quad (98)$$

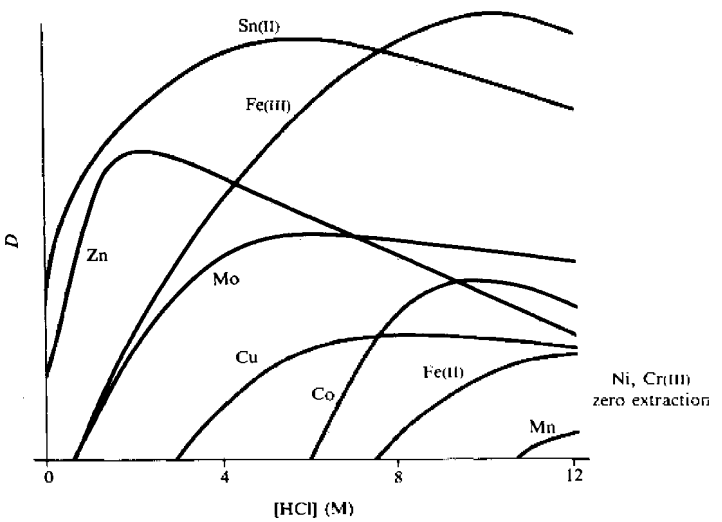


Figure 12 Volume-distribution coefficients in hydrochloric acid for various elements on the strong-base anion-exchange resin Dowex 1 X-10 (after Krause and Moore, ref. 359)

The greatest potential use of anion-exchange resins in hydrometallurgy obviously lies in the treatment of sulfate, chloride and cyanide leach liquors in which the anionic ligands form strong metal complexes. An example of the selectivity that can be achieved with a strong-base resin in chloride solution is shown in Figure 12. Tin, zinc, iron and molybdenum all form strong anionic chloro complexes, even in fairly dilute chloride solution, and copper and cobalt form anionic complexes of intermediate strength. Nickel does not form anionic chloro complexes, while trivalent chromium is kinetically inert to chloride attack. It can be seen that by careful control of the chloride concentration in the range 0–10 M excellent separations of these metals, and many others (Figure 13), can be achieved.

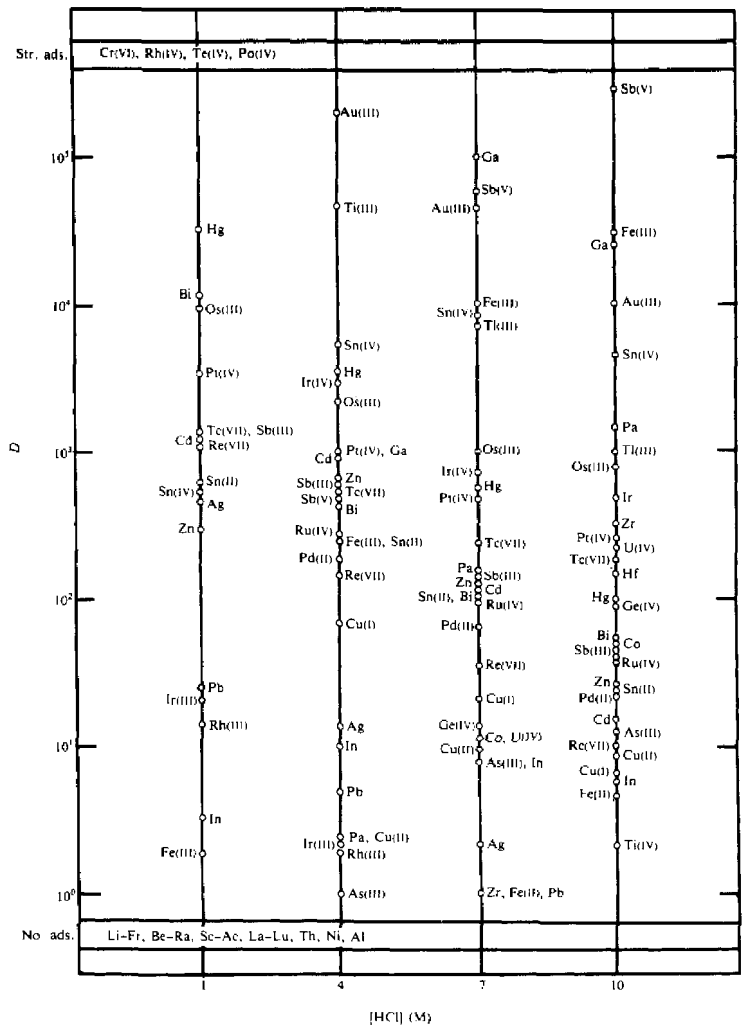


Figure 13 The distribution of various ions between aqueous hydrochloric acid solution and a strong-base resin, Dowex 1 X-10, as a function of hydrochloric acid concentration (after Marcus and Kertes, ref. 132)

Far less selectivity can be achieved in cyanide solution because many metals, both precious and base, form anionic complexes in even very dilute cyanide solution. This is illustrated by the equilibrium absorption isotherms for various metal ions in a leach liquor from a gold cyanidation plant on a strong-base resin (Figure 14).[358]

Owing to the wide variation in the strength of the metal cyanide complexes that occur commonly in leach liquors from gold plants, some degree of selectivity can be achieved by adjustment of the pH value of the solution. The aurocyanide anion ($\log\beta_2 = 47$) is far more stable than the ferrocyanide ($\log\beta_6 = 36$), nickel cyanide ($\log\beta_4 = 30$), copper(I) cyanide ($\log\beta_4 = 28$) and zinc cyanide ($\log\beta_4 = 19$) complexes, and remains in solution as an anion at pH values at which the other anions decompose. This is illustrated by the curves shown in Figure 15;[358] the effect of pH on the selectivity of a strong-base resin for metal cyanide complexes is shown in Figure 16.[358]

It has also been shown[360] that the selectivity of anion-exchange resins for monovalent anions over polyvalent anions is a function of the distance by which the fixed charges on the resin matrix are separated. The uptake of a divalent anion requires the presence of two closely spaced positive

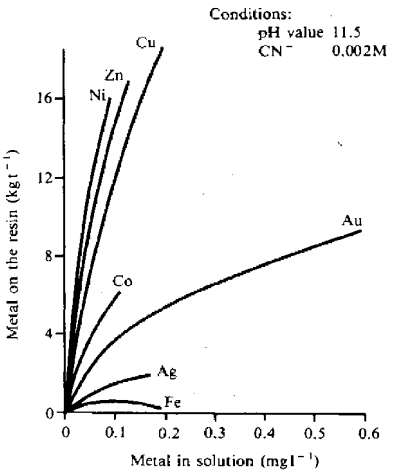


Figure 14 The equilibrium loading of various metal cyanide complexes from a gold plant pregnant solution onto a strong-base resin (A101DU) (after Fleming and Cromberge, ref. 358)

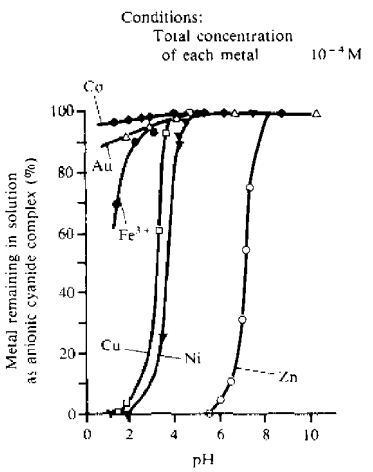


Figure 15 The effect of acidity on the stability of various metal–cyanide complexes in aqueous solution (after Fleming and Cromberge, ref. 358)

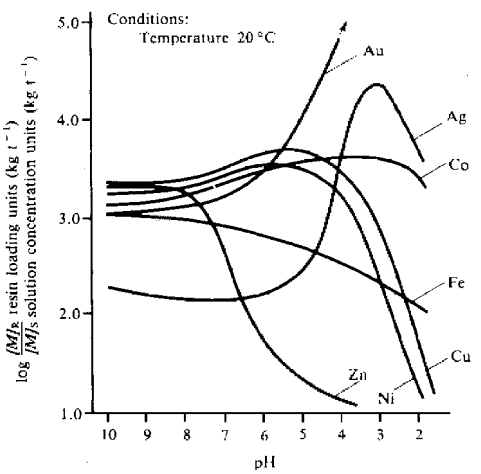


Figure 16 The effect of pH on the selectivity of a strong-base resin (A101DU) for metal cyanide complexes (after Fleming and Cromberge, ref. 358)

charges, whereas no such constraints exist in the extraction of monovalent anions. Results presented recently[358] have shown that the application of this theory to the extraction of metal anions from cyanide solution by weak-base resins allows for greatly improved selectivity for the monovalent gold and silver cyanide complexes. With increasing pH of the solution, the number of ionized functional groups in a weak-base resin decreases, and the average distance between adjacent ionized groups increases, improving the selectivity of the resin for monovalent anions. This is illustrated by the results in Table 4 in which the absorption properties of two commercial weak-base resins (A7, made by Duolite International and IRA 93, made by Rohm and Haas) are compared with those of a strong-base resin (A101DU, made by Duolite International), at two pH values.

Most weak-base resins have a low and variable concentration of permanently charged functional groups in the resin matrix. These pseudo strong-base groups arise as a result of the crosslinking of adjacent amine groups, and have all the properties of the quaternary amine groups of strong-base resins. Russian workers[361] have observed that certain weak-base resins with a low strong-base content extract gold very selectively from cyanide solutions of high pH, but that the selectivity disappears if the strong-base content exceeds about 20% of the total resin capacity. The mechanism of rejection of the multivalent complex cyanide anions in this instance is presumably also based on the charge separation theory.

(ii) Applications

(*a*) *Uranium.* By far the most important contribution of ion-exchange resins in hydrometallurgy has been in the extraction of uranium. By the late 1940s most of the world's uranium was extracted

Table 4 The Distribution of Anionic Metal Cyanide Complexes Between Anion-exchange Resins and an Aqueous Cyanide Solution as a Function of Solution pH[a]

Metal cyanide anion	*A7*		*IRA 93*		*A101DU*	
	D_{11}	D_6	D_{11}	D_6	D_{11}	D_6
Gold	71	1140	3230	3440	18950	16750
Silver	90	150	210	280	2210	190
Cobalt	120	600	170	4870	21170	15530
Copper	20	650	100	1040	3880	2050
Nickel	10	1460	510	3920	24400	10180
Iron	115	1160	240	4250	4260	8520
Zinc	13370	8130	1080	520	46000	3080

[a] D_{11} and D_6 = distribution coefficients at pH = 11 and 6 respectively. Concentration of metal in solution $\approx 10^{-4}$ M (from Fleming and Cromberge, ref. 358).

from low-grade ores (0.05–0.5% uranium), which were leached with sulfuric acid. These solutions contained high concentrations of free sulfuric acid, iron, aluminum, vanadium, magnesium, calcium, titanium and silica, and uranium-recovery techniques such as precipitation with ammonia or extraction with cation-exchange resins were so unselective that the purity of the final uranium product was often not much better than the original ore. Only when it was observed for the first time in the early 1950s that the uranyl ion undergoes stepwise formation of anionic complexes with sulfate or bisulfate

$$UO_2^{2+} + nSO_4^{2-} \rightleftharpoons UO_2(SO_4)_n^{2-2n} \tag{99}$$

$$UO_2^{2+} + nHSO_4^{-} \rightleftharpoons UO_2(SO_4)_n^{2-2n} + nH^{+} \qquad (n = 1, 2, 3) \tag{100}$$

were anion-exchange resins used for the first time, allowing uranium to be concentrated and separated from the major impurities in sulfuric acid leach liquors. Fixed-bed anion exchange became the universally accepted means for the recovery of uranium in the 1950s, and it also represented the only large-scale hydrometallurgical application of ion exchange. In the 1960s and early 1970s a move was made towards solvent extraction with tertiary amines because this technique offered improved selectivity and because it could be operated as a sophisticated continuous process, whereas fixed-bed ion exchange was traditionally a batch operation. With the development in the 1970s of several elegant continuous ion-exchange processes, the pendulum swung back to ion exchange to a certain extent, and the modern trend is generally for very low-grade solutions (with a uranium content of less than 200 mg l^{-1}) to be treated by ion exchange, and for higher-grade solutions to be treated by solvent extraction. On a number of plants in South Africa the so-called Bufflex process employs ion exchange and solvent extraction back-to-back. In this process a low-grade, unclarified, leach liquor is first concentrated by a strong-base resin, and the concentrated eluate from the ion-exchange process is then purified in a small solvent-extraction plant. As the demand for products of higher purity and the need for the processing of lower-grade ores increases, this type of process is likely to become more popular.

There are several uranium ore-bodies in the world that cannot be leached economically with sulfuric acid because of the high limestone content of the ore. Such ore-bodies are generally leached with an alkaline solution of sodium carbonate and bicarbonate. Carbonate also forms anionic complexes with the uranyl ion — the predominant species being $UO_2(CO_3)_3^{4-}$ — and may therefore also be treated with anion-exchange resins.

The leaching reactions and the distribution of the various anionic uranyl species are very dependent on the pH value of the leach liquor and on the sulfate or carbonate concentration. Nominally, only the anionic di- and tri-sulfate or carbonate species will exchange with the functional groups of an anion-exchange resin, but the resin itself can facilitate the formation of complex anions in the resin phase because of the high concentration (approximately 0.5 M) of the co-ion on the functional group. Therefore, a complex equilibrium is established in which the resin is a participant; the following reactions describe these equilibria for sulfuric acid leach liquors:

$$(|\!-\!\overset{+}{N}R_3)_2SO_4^{2-} + UO_2SO_4 \rightleftharpoons (|\!-\!\overset{+}{N}R_3)_2UO_2(SO_4)_2^{2-} \tag{101}$$

$$2(|\!-\!\overset{+}{N}R_3)_2SO_4^{2-} + UO_2(SO_4)_2^{2-} \rightleftharpoons (|\!-\!\overset{+}{N}R_3)_4UO_2(SO_4)_3^{4-} + SO_4^{2-} \tag{102}$$

$$2(|\!-\!\overset{+}{N}R_3)_2SO_4^{2-} + UO_2(SO_4)_3^{4-} \rightleftharpoons (|\!-\!\overset{+}{N}R_3)_4UO_2(SO_4)_3^{4-} + 2SO_4^{2-} \tag{103}$$

The affinity of a strong-base resin for various anions commonly present in uranium process solutions can be ranked as follows: $UO_2(SO_4)_3^{4-} > UO_2(SO_4)_2^{2-} > NO_3^- > Cl^- > HSO_4^- > Fe(SO_4)_2^- > SO_4^-$.

In the 1950s, uranyl sulfate was stripped from the strong-base resins with a concentrated solution of chloride or nitrate, these being the two most efficient anions in the above sequence. Uranium was recovered from the strip solution by precipitation of the diuranate species with ammonia:

$$2H_2[UO_2(SO_4)_3] + 14NH_4OH \longrightarrow (NH_4)_2U_2O_7 + 6(NH_4)_2SO_4 + 11H_2O \quad (104)$$

On the modern plants employing the Bufflex flowsheet, uranyl sulfate is stripped from the resins with the bisulfate anion. The eluate contains about 1 M sulfuric acid since this is the optimum concentration for the subsequent solvent-extraction process; at lower acid concentrations, the tertiary amine in solvent extraction is only partially ionized, which reduces its capacity for uranyl sulfate, whereas at higher acid concentrations the bisulfate anion begins to compete with the uranyl sulfate anion for tertiary amine functional groups.

In the alkaline process, uranyl carbonate is eluted from the resin by concentrated (approximately 1 M) solutions of chloride, carbonate or bicarbonate, and is recovered from the eluate by treatment with an acid to destroy the carbonate complex, followed by precipitation of the diuranate, *e.g.*

$$(NH_4)_4[UO_2(CO_3)_3] + 6HCl \longrightarrow 4NH_4Cl + UO_2Cl_2 + 3H_2O + 3CO_2 \quad (105)$$

$$2UO_2Cl_2 + 6NH_4OH \longrightarrow (NH_4)_2U_2O_7 + 4NH_4Cl + 3H_2O \quad (106)$$

Weak-base resins have been tested from time to time but have not found wide acceptance in the uranium industry. The main reason for this is that the major advantage of weak- over strong-base resins, *viz.* elution by neutralization, cannot be utilized in uranium processing since it is not possible for the weak-base resin to be converted to the free-base form without diuranate precipitating within the pores of the resin (unless a complexing agent such as carbonate is added to the eluate). In the presence of carbonate, uranium remains in solution as the uranyl carbonate anion, even in very alkaline solution, so is readily eluted from a weak-base resin in the free-base form. This eluate would then be treated as depicted in equations (105) and (106) for the recovery of uranium. Alternatively, weak-base resins can be eluted by ion-exchange mass action.

(b) Gold. The conventional process for the recovery of gold involves oxidative leaching with oxygen in calcium cyanide solution to produce a very dilute (usually less than 10 mg l^{-1}) solution of gold as the anionic complex $Au(CN)_2^-$. The leach liquor is then filtered and treated with zinc powder to reduce the gold back to the metallic state. Although the zinc-precipitation process is simple and cheap, and the technology is well-developed, there are certain instances when an anion-exchange concentration and purification step may be profitable. For example, the chemical composition of the leach liquor occasionally does not lend itself to the quantitative or economic recovery of gold by zinc cementation (a very low gold concentration or very high impurity concentration, for example), but the major potential application of anion-exchange resins in gold processing is for the recovery of aurocyanide direct from the pulp in the resin-in-pulp (RIP) process. The filtration and clarification steps are a very costly component of the conventional gold process, especially with certain ores that are difficult to filter, and it is likely that the RIP process would offer significant cost advantages in most applications.

RIP for the recovery of gold and silver from cyanide pulp was proposed in South Africa in 1960,[362] and pilot-plant tests were carried out at that time. More recent progress in the development of RIP for gold extraction has come from the Soviet Union,[363,364] and a 1978 report[365] indicates that one of the largest gold mines in the Soviet Union is using anion-exchange resins to extract aurocyanide in an RIP plant. This is believed to have been the world's first application of RIP to gold extraction, although RIP is now used widely for gold extraction in the Soviet Union.[365] The whole question of the recovery of gold from solutions or pulps by resins recently came under close scrutiny in South Africa[358,366–368] but, although the process looks promising, no gold mines outside the Soviet Union have implemented this technology. The close association of gold and uranium in many of South Africa's gold-bearing reefs, and the success of the continuous ion-exchange process for the recovery of uranium from these ores, has also led to research and pilot-plant studies on an integrated anion-exchange RIP process for the recovery of both gold and uranium.[369]

In the extraction process, the aurocyanide complex plus other metal cyanide complexes that are common in cyanide leach liquors (*e.g.* $Fe(CN)_6^{4-}$, $Fe(CN)_6^{3-}$, $Zn(CN)_4^{2-}$, $Ni(CN)_4^{2-}$, $Cu(CN)_4^{3-}$ and $Co(CN)_6^{3-}$) load onto the resin by simple ion exchange:

$$n|—\overset{+}{N}R_3X^- + M(CN)_x^{n-} \rightleftharpoons (|—\overset{+}{N}R_3)_nM(CN)_x^{n-} + nX^- \quad (107)$$

Because of their symmetry, high polarizability and multiple anionic charge, these complexes are generally very strongly bound to the resin, and elution, particularly from strong-base resins, is difficult. Anions such as chloride, bisulfate, nitrate or cyanide can be used to reverse the equilibrium shown in equation (107) but, only when the activity of these anions is increased by the addition of a polar organic solvent such as acetone or acetonitrile to the eluate, are reasonable rates of elution achieved. This forms the basis of the organic type of elution procedures that were tried in the past.[370] Two anions that absorb very strongly onto anion-exchange resins that have been shown[366] to be very effective eluants for aurocyanide, even in aqueous solution, are the thiocyanate and zinc cyanide anions. Because they absorb so strongly onto the resin, the resin must be regenerated before recycling to extraction. For the zinc cyanide complex, this is achieved effectively and cheaply by destruction of the complex with acid:

$$(|—\overset{+}{N}R_3)_2Zn(CN)_4^{2-} + 2H_2SO_4 \longrightarrow (|—\overset{+}{N}R_3)_2SO_4^{2-} + ZnSO_4 + 4HCN \quad (108)$$

The removal of thiocyanate from a strong-base resin can be achieved effectively by treatment with an iron(III) salt.[366] In the presence of a slight excess of Fe^{3+} ions, thiocyanate forms the cationic complexes $FeSCN^{2+}$ and $Fe(SCN)_2^{+}$:

$$2|—\overset{+}{N}R_3SCN^- + Fe_2(SO_4)_3 \longrightarrow (|—\overset{+}{N}R_3)_2SO_4^{2-} + 2[FeSCN]SO_4 \quad (109)$$

Thiocyanate can be recovered and recycled from this solution by the precipitation of iron as iron(III) hydroxide.[366] Aurocyanide can also be eluted from a strong-base resin by chemical conversion of the gold to a cationic complex with the thiourea ligand, as shown above (equation 98). This method of gold elution is favoured in the Soviet Union, but suffers from the drawback that elution of the other metal cyanide complexes is generally poor, and multi-elution procedures are necessary.

The elution of aurocyanide and other anions from a weak-base resin is achieved by neutralization of the amine functional groups (equation 96). The method is cheap and very effective;[366] this is a major factor favouring the use of weak-base resins, particularly since recent research has shown that modern weak-base resins extract aurocyanide efficiently from cyanide leach liquors that have undergone minimal adjustment of pH.[358,368]

(c) Silver. Until relatively recently, a considerable amount of silver from secondary sources such as plating or photographic wastes was discharged in waste streams. In plating waste, silver is generally present as the anionic cyanide complex $Ag(CN)_2^-$, and in photographic waste it is present as the anionic thiosulfate complex $AgS_2O_3^-$. Therefore anion exchange offers relatively inexpensive technology for the recovery of silver from these sources, and considerable research has been done on the development and installation of resin processes for this application.[371–373] Both strong- and weak-base resins have been used successfully, weak-base resins generally being preferred because of the greater ease with which they are eluted. Strong-base resins are eluted with cyanide, thiocyanate or thiosulfate,[373] and silver is recovered from the eluate by electrolysis.

(d) Platinum-group metals. The platinum-group metals (PGM) all form stable anionic complexes in choride solution ($PtCl_4^{2-}$, $PtCl_6^{2-}$, $PdCl_4^{2-}$, $IrCl_6^{2-}$, $IrCl_6^{3-}$, $RhCl_6^{3-}$, $RuCl_6^{2-}$, $RuCl_6^{3-}$ and $OsCl_6^{2-}$). The various complexes are extracted quantitatively by anion-exchange resins, but some degree of separation can be achieved with selective elution techniques.[374] Anion-exchange resins are, however, generally used only in the recovery and concentration of PGM (particularly platinum) in secondary sources such as plating wastes. Solvent extraction is currently preferred for the treatment of PGM concentrates because of the high concentration of metal in solution and the cleaner separations that can be achieved with solvent-extraction reagents.

63.3.3.3 Chelating resins

Metal ions are adsorbed onto chelating resins from aqueous solution by a mechanism similar to that shown above for cation-exchange resins (equation 92). However, the exchange of metal cations in solution with protons on the resin does not involve dehydration of the metal ion for cation-exchange resins, but for chelating resins it does, and the metal cation is bound in the resin phase by a combination of outer-sphere ionic and inner-sphere covalent forces:

$$M(H_2O)_x^{n+} + n|—RH \rightleftharpoons (|—R)_nM(H_2O)_{x-n} + nH^+ \quad (110)$$

The coordination of all vacant valencies in the metal ion results in a very strong bond, and this, in turn, ensures far greater selectivity than can be achieved with cation-exchange resins. In cation-exchange resins, bond energies of the order of 8 kJ mol^{-1} are fairly representative for simple

divalent ions, whereas bond energies five to 10 times higher are common in chelating resins. This is illustrated by the results in Table 5.

Table 5 Formation Constants and Bond Energies of Formation in the Interaction of Various Metal Cations with Cation-exchange and Chelating Resins

Complex formed in resin phase	*Metal ion*	*Stability (log K)*	*Bond energy* (ΔG_f°; kJ mol^{-1})
2:1 ion-pair	Ca^{2+} (OH^-)	1.4	7.9
2:2 ion-pair	Ca^{2+} (SO_4^{2-})	2.3	13.4
Dicarboxylic acid	Ca^{2+}	2.5	14.2
	Fe^{2+}	2.8	15.9
	Ni^{2+}	4.1	23.4
	Cu^{2+}	5.5	29.3
8-Hydroxyquinoline chelate	Fe^{2+}	9.8	56.4
	Zn^{2+}	10.9	62.7
	Co^{2+}	10.9	62.7
	Ni^{2+}	11.7	67.3
	Cu^{2+}	15.0	86.1
Aminodiacetate chelate	Ca^{2+}	10.6	60.6
	Co^{2+}	16.1	92.0
	Ni^{2+}	18.4	105.8
	Cu^{2+}	18.3	105.3

[a] From Kitchener, ref. 375.

All transition metals are known for their ability to form strong coordination compounds, and very good selectivity for transition metals over non-transition metals can be achieved with all the chelating resins on the market. Reasonable selectivity for one or more metals within a series of transition metals can also be achieved, since theoretical considerations derived from valence-bond theory and experimental analytical evidence predict that the stability constants of metal complexes will depend primarily on the electronic configuration of the metal and only to a minor extent on the ligand. For example, an approximately linear relationship has been established between metal stability constants (with more than 100 ligands) and the sum of the first and second ionization potentials of the metal, the ionization potential being a measure of the tendency of the metal to accept electrons from the ligand. Unlike simple anion- and cation-exchange resins, the size and charge of the metal ions play little part in determining selectivity. In the first transition series, the strength of the coordination compounds almost invariably increases according to the well-known Irving–Williams series, $Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$, and most chelating resins will extract cations in this order. Therefore, copper can be extracted selectively from a solution containing manganese, iron, cobalt, nickel and zinc with most chelating resins, or nickel can usually be extracted fairly selectively provided no copper is present. To find a ligand that reverses this general trend at any stage and to incorporate that ligand into a polymeric matrix is far more difficult, and is a task that has challenged and intrigued chemists for several decades. For example, over the years, a number of research workers[376,377] have attempted to incorporate the well-known nickel-specific ligand dimethylglyoxime into a polymeric matrix, and although nickel-selective resins based on this ligand have been made, they have suffered from other problems, such as the hydrolytic stability of the ligand functional group or low capacity.

The history of the early development of chelating resins was reviewed in 1957,[378] and a recent study[379] describes the important developments from 1957 to the present time; only those developments that are likely to make a contribution in large-scale hydrometallurgical processing will be discussed here, however.

The first chelating resins that were found to be really suitable for application in the field of selective cation absorption were those based on the aminodiacetate functional group.[380] The first commercial resin based on this functional group, Dowex A1, was shown[381] to have an affinity for a range of metals which was similar to the order of dissociation constants of the metal complexes with ethylenediaminetetraacetic acid (EDTA), *i.e.*

Resin selectivity	Sr	<	Ca	<	Fe	<	Co	<	Zn	<	Ni	<	Pb	<	Cu
K_{EDTA}	8.6		10.7		14.3		16.3		16.5		18.6		18.0		18.7

Moreover, the range of stability constants was some three orders of magnitude greater than that of an ordinary sulfonic acid. Since then, many research groups have made resins based on the

aminodiacetate functional group, some of which have interesting metallurgical properties. In general, the order of affinity between polymer and transition metal ions is similar for all the polymers based on this functional group, and improved selectivities can only be achieved at the expense of the large binding constants typical of aminodiacetate or diaminotetraacetate resins.[379]

Other types of resin, incorporating oxygen as well as nitrogen functional groups, have been developed in an attempt to reproduce the sort of metallurgical performance that has been achieved with analogous solvent-extraction reagents, such as the LIX reagents based on hydroxyoxime groups. For the most part, the performance of these resins has been disappointing and they have suffered from problems with capacity or selectivity, or both.[379]

One of the most obvious applications of chelating resins is in the selective extraction of copper from low-grade leach liquors. The hydrometallurgical processing of low-grade copper ores is confined almost exclusively to leaching with sulfuric acid and, although these solutions contain copper at levels from a few grams per litre down to 0.1 g l^{-1}, the application of conventional processes (such as cementation or solvent extraction) has been restricted to solutions containing at least 1 g l^{-1}. Ion-exchange processes would open the way to the treatment of lower-grade ores and solutions, and will inevitably become more attractive as the richer copper ore-bodies become depleted. Another potential application for the future is in the treatment of barren solutions on uranium plants. These dilute sulfuric acid solutions contain copper, nickel and cobalt at concentrations ranging from 0.05 to 1 g l^{-1} and the extraction of cobalt and nickel from such solutions could become an attractive proposition.

These copper and uranium leach liquors generally contain high concentrations of Fe^{3+} ion, and a major limitation of all the earlier chelating resins in these applications was their poor selectivity for copper, nickel or cobalt over Fe^{3+} ions, and their low exchange capacity at the pH values typical of these leach liquors. However, several resins have been introduced recently that show good selectivity for copper over iron and absorb copper well at pH values around 2. These are the Dow picolylamine derivative resins, XFS 4195, XFS 4196 and XFS 43084.[382] Their good selectivity for copper is attributed to the fact that copper forms a covalently bonded five-membered ring complex with the picolylamine group, whereas iron is loaded by an ion-exchange mechanism, forming a weak electrostatic bond between the iron(III) sulfate anion $Fe(SO_4)_2^-$, and the protonated amine, analogous to that in a weak-base anion-exchange process.[383] The selectivity of these resins for copper over iron therefore deteriorates with increasing acidity.

A similar selectivity for copper over Fe^{3+} ions was observed for the recently described pyridylimidazole derivative resins, PI1 and PI2.[384] There, too, iron is believed to be loaded onto the resin as the $Fe(SO_4)_2^-$ anion, and it was shown[383] that a six-fold improvement in the selectivity for copper over iron resulted when the aqueous-solution anion was changed from sulfate to nitrate, which does not form anionic complexes with Fe^{3+} ions.

Table 6 Metal Ion Absorption by XFS 43084 Resin[a, b]

Species	*pH*	*Equilibrium conc.* (g l^{-1}) *Solution*	*Resin*	*K* (1 mol^{-1})
Cu	2.1	0.68	30	500
Fe^{III}	2.0	0.87	8.6	18
Ni	2.0	0.80	10.1	29
	3.0	0.75	16	64
Co	2.2	0.93	1.7	3.2
	3.5	0.85	8.4	22
Cd	2.2	0.89	0.3	0.6
	5.0	0.87	3.3	7.2
Zn	2.2	1.06	1.0	1.5
	3.6	0.98	7.1	14
Al	3.7	0.71	0.3	0.7
Mg	6.3	0.90	0.33	0.6
Ca	6.3	0.19	0.38	3.2
Fe^{II}	2.2	1.25	0.14	0.18
	4.0	1.13	2.1	3.1

[a] Resin solution volume ratio = 1.2/100, initial aqueous concentrations of metal ion 1 g l^{-1}, except Ca, which was 0.2 g l^{-1}, $K = [\overline{M}]/\{[M^{n+}][\overline{RH}]\}$ where bars denote the resin phase and $\overline{RH}$ represents the free functional-group concentration at equilibrium.
[b] From Grinstead, ref. 382.

At higher pH values, the picolylamine and pyridylimidazole resins also absorb other base metals in the first transition series, and useful separations can be achieved. This is illustrated by the results

in Table 6,[382] which refer to the Dow resin XFS 43084. In particular, nickel can be extracted selectively from cobalt solutions with both types of resin, and this property could be applied usefully in the cobalt electrowinning industry, for example, where it is important for the nickel concentration in the advance electrolyte to be kept very low.

Most transition metals form their strongest complexes with ligands carrying oxygen or nitrogen as donor atoms. There is a small group of ions, however, including Pd^{2+}, Pt^{2+}, Au^{+}, Ag^{+}, Cu^{+} and Hg^{2+}, which form their most stable complexes with donor atoms such as phosphorus, sulfur and arsenic. Several resins based on sulfur donor atoms have been prepared; these include mercapto,[385] thioglycolate[386] and dithiocarbonate[387] functional groups. The interest in polymers of this type has been mainly in pollution-abatement and analytical applications. Two resins that extract the noble metals (the PGM plus gold) very selectively[388] and that are based on the polyisothiouronium group have been shown[379,389] to extract the metals by anion exchange with the weak-base amine groups and by coordination with the sulfur donor atoms.

The covalent bond formed between precious metals (PGM, gold and silver) and functional groups with a sulfur donor atom are often so strong that elution without destruction of the resin is generally difficult. In such cases, because of the very high capacity of these resins and because of the value of the metal loaded, incineration of the resin is usually the most economically viable method for recovery of the precious metals.

63.3.3.4 Future trends

(i) Solvent-impregnated resins

The solvent impregnation of resins is a relatively new concept that has developed from a growing awareness of the need for ion-selective resins, and the slow development of such resins caused by fundamental difficulties in the attachment of the selective functional groups to polymers. The concept of a solvent-impregnated resin (SIR) is a compromise which seeks to eliminate the disadvantages inherent in solvent-extraction and ion-exchange processes, and consolidate their respective advantages. In an SIR, the organic ligand is physically absorbed into the pores of an inert polymer without undergoing chemical bonding to the polymer. It therefore combines the advantageous chemical properties of the solvent-extraction reagent, such as high mass-transfer rates, high capacity and good selectivity, with the physical advantages of ion-exchange resins, such as low losses of solvent and simpler organic–aqueous engagement and disengagement. Two approaches for the incorporation of organic reagents into inert polymers have been developed. The first approach, which is based on the physical absorption of the extractant into a high-surface macroporous polymer bead,[390] can be applied universally to many reagents and polymers.[391] An SIR prepared in that way by the impregnation of hydroxyoxime into a neutral polymeric support has been shown[392] to retain the distinctive properties of the reagent with very good selectivity for copper over other divalent ions and iron(III). Another series of SIRs, which incorporated phosphoric acid or phosphonic ester compounds, retained the distinctive features of the reagents and were able to extract trace quantities of zinc from cobalt sulfate solutions.[393] The second approach in the development of SIRs, which was pioneered by the Bayer AG Company, employs the incorporation *in situ* of the extractant during the copolymerization process.[394] These SIRs are termed Levextrel resins and ligands that have been incorporated into this type of resin include phosphoric acids and esters for the removal of heavy metals from solution.[395]

An interesting property of resins impregnated with oximes or oxines is that the selectivity of, for example, copper over iron(III), approaches that of a pure solvent-extraction process only when an inert solvent is present in the pores of the resin.[396] Thus, in a β-hydroxyoxime SIR, the selectivity for copper over iron(III) improved by a factor of 20 when the solvent perchloroethylene was introduced into the SIR, and by a factor of 700 in a similar resin impregnated with 8-hydroxyquinoline.[396] This is believed to be due to kinetic and thermodynamic restrictions in the extraction of iron(III), but not of copper, at an aqueous–organic boundary.[396,397]

The only major impediment to the development of SIRs on an industrial hydrometallurgical scale is the problem of leakage of the reagent from the resin phase into the aqueous feed solution, a problem that is more severe in the first type of SIRs than in the Levextrel resins. If this problem can be solved, a bright future is predicted for this concept in resin technology.

(ii) Ion exchange in non-aqueous media

Ion exchange from organic solvents and mixed organic aqueous solvents offers interesting possibilities for the extraction and separation of metals because of the different nature of the solvation processes in these systems. Only cation solvation is significant in dipolar, aprotic, organic

solvents,[398] and the anions are relatively more reactive than in water, allowing for enhanced distribution coefficients with anion-exchange resins.

As the ratio of organic to aqueous in a mixed solvent is increased, the concentration of water molecules around the cation is reduced, decreasing the size of the hydrated cation. One consequence of this is that metal complex anions will be formed at lower anion concentrations than in pure water. Moreover, because the forces that bind the hydration cloud depend on the charge density of the cation, selective destruction of the hydration cloud starts at lower organic : aqueous ratios for larger cations.[399] As a result, large cations will penetrate a cation exchanger more easily, and differences in the distribution coefficients of elements of different size will be enhanced.

Selectivities of potential hydrometallurgical interest that were demonstrated recently[400] are the very good extractions of nickel and cobalt from acetonitrile, propylene carbonate, sulfolane or dimethylformamide by a cation exchanger; copper, iron(II), iron(III) and zinc, present in the same solution, are either weakly extracted or are not extracted at all. It is also possible for copper to be extracted selectively from Fe^{3+} ions with an anion exchanger in dimethyl sulfoxide, dimethylformamide or dimethylacetamide.[400]

63.3.4 Precipitation

The recovery or removal of metals from solutions derived from the leaching of minerals is an important step in any hydrometallurgical process. Precipitation by reduction to the metallic state in electrochemical cells will be discussed in Section 63.3.5; this section will cover the use of chemical reagents to control the precipitation process. Therefore, although the production of metallic powders by the reduction of metal ions with hydrogen or less-noble metals (cementation) is electrochemical in nature, it will be discussed under this heading.

63.3.4.1 Oxides

The selective hydrolysis of metal ions to produce various forms of hydrated oxides is the most widely used form of precipitation. In particular, the removal of iron from hydrometallurgical process streams is a continuing problem. Iron enters the circuit as a constituent of a valuable mineral, such as chalcopyrite ($CuFe_2$), or an impurity mineral, such as the ubiquitous pyrite or pyrrhotite. So far, effective removal of the iron has been achieved by the precipitation of iron(III) as jarosite ($MFe_3(SO_4)_2(OH)_6$),[401] goethite ($FeOOH$)[402] or hematite (Fe_2O_3).[403]

The fundamental chemistry associated with the thermodynamics of formation of the alkali jarosites (M = Na, K or NH_4) has been studied,[404] and it has been found that substitution of the alkali ions by Ag^+ or 1/2 Pb^{2+} produces jarosites that are often formed during the processing of lead or zinc ores, which generally contain silver as a valuable byproduct. In addition, partial or complete substitution of iron(III) by divalent metal ions can occur, resulting in the formation of an extensive range of substituted jarosites such as beaverite, $PbCuFe_2(SO_4)_2(OH)_6$. The order of incorporation into the lead jarosite structure has been found to be $Fe^{3+} \gg Cu^{2+} > Zn^{2+} > Co^{2+} > Ni^{2+} > Mn^{2+}$. This order appears to be related roughly to the ease of hydrolysis of the various cations, and this knowledge has been of considerable use in the rationalization of the loss of valuable metals such as copper, zinc, cobalt and nickel in the jarosites that are formed during the iron-removal steps. This is particularly severe for gallium(III) and indium(III), which can replace all the iron and thus be lost as byproducts. The partition coefficient for gallium is significantly higher than that for aluminum, presumably because gallium is more similar in size to iron(III) than aluminum. A knowledge of the thermodynamics of the formation of the various hydroxy and sulfato complexes of iron(III), especially at elevated temperatures, has been invaluable in the establishment of the optimum conditions for the precipitation of goethite and hematite.[405] The results of calculations of the solubility of the various oxides and basic sulfates are often demonstrated by the use of predominance-area (or volume) diagrams, an example of which is given in Figure 17. The dotted lines represent equal concentrations of neighbouring complexes and hence define areas of predominance for each species. Solutions with compositions above the solid line are unstable with respect to the precipitation of goethite. The effect of complexing by sulfate on the equilibria can be calculated, and a third dimension, *viz.* sulfate concentration, can be incorporated in the diagram.

Another process that has benefited from procedures such as that outlined above is the removal of cobalt from leach liquors derived from the extraction of nickel-bearing concentrates or mattes.[406] Traditionally, the removal of cobalt from such acidic sulfate solutions has been based on the affinity of the trivalent metal ions (such as those of iron and cobalt) for hydroxide, which

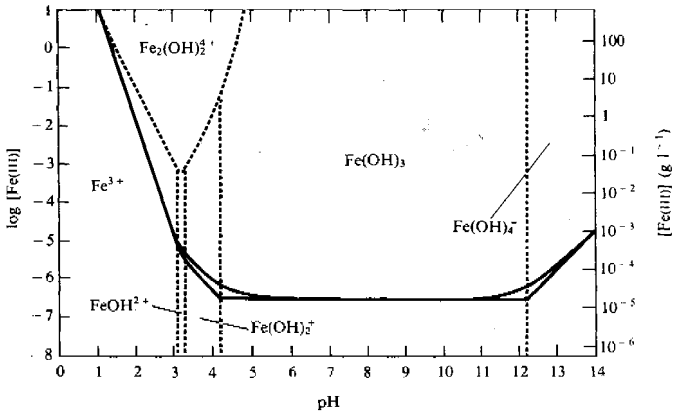


Figure 17 Solubility of FeOOH at 25 °C (after McAndrew, Wang and Brown, ref. 405)

is well known to be greater than that of the divalent metal ions. Hence, by the appropriate choice of pH and the oxidizing agent, cobalt(II) can be effectively removed as the cobaltic oxide trihydrate $Co_2O_3 \cdot 3H_2O$. At present, most commercial operations use either chlorine or nickel(III) compounds, the latter being prepared by the electrolytic oxidation of alkaline nickel(II) hydroxide:

$$Ni(OH)_2 + OH^- \longrightarrow NiOOH + H_2O + e^- \quad (111)$$

$$NiOOH + Co^{2+} + 3H_2O \longrightarrow Co(OH)_3 + Ni(OH)_2 + 2H^+ \quad (112)$$

It is likely that developments in cobalt-selective reagents, such as those outlined in Section 63.3.2.2, will result in this approach being replaced by solvent extraction in the future.

63.3.4.2 Sulfides

Most base-metal sulfides are very insoluble compounds and, in principle, processes based on the differences in their solubilities can be used in the selective precipitation of sulfides. For example, the strong affinity of copper ions for sulfide ion is used to good effect in the removal of traces of copper from leach liquors in the recovery of nickel,[406] cobalt[407] and manganese.[408] For manganese, other impurity metal ions such as cobalt, nickel and zinc are also selectively precipitated by the use of sulfide ions.

An interesting application[409] of the use of sulfide ion as a selective precipitant for metals is the removal of molybdenum in the commercial recovery of tungsten from low-grade scheelite (calcium tungstate) concentrates. In this process, dissolution of the tungsten as soluble tungstate and of the molybdenum as molybdate ions is achieved by a pressure-leaching procedure using sodium carbonate. The molybdate ions are then selectively converted to the thiomolybdate species by the addition of excess sulfide ions:

$$MoO_4^{2-} + 4HS^- \longrightarrow MoS_4^{2-} + 4OH^- \quad (113)$$

Although thermodynamically possible, the slower rate of substitution of the tungsten(VI) species results in the formation of only a small amount of the corresponding thiotungstate ion, provided that the conditioning period with sulfide ion is controlled. Molybdenum trisulfide is then quantitatively precipitated by the decomposition of the thio salt by the slow addition of sulfuric acid to a pH value of between 2 and 3:

$$MoS_4^{2-} + 2H^+ \longrightarrow MoS_3 + H_2S \quad (114)$$

Under carefully controlled conditions, the filtrate contains less than 10 mg of molybdenum per litre, and the precipitate less than 1% of the tungsten. Osseo-Assare,[410] with a knowledge of the stabilities of the various species involved, recently subjected this process to a thermodynamic analysis.

63.3.4.3 Metals

The possibility that reducing gases such as sulfur dioxide, carbon monoxide or hydrogen can be used under pressure to effect the final precipitation of metals from their solutions is an obvious and, in some instances, an attractive alternative to electrowinning or cementation.[411] Of the commercial plants built to produce metals in powder form by gaseous reduction of the metals from

aqueous solutions, those based on the Sherritt Gordon ammoniacal pressure leach process[32] have been the most successful, and continue to be built and operated. These plants produce nickel powders and small quantities of special copper powders by the reduction with hydrogen of the metals from their ammine sulfate solutions.

The overall reaction for the reduction of nickel from ammoniacal solutions with hydrogen under pressure can be written as

$$Ni(NH_3)_x^{2+} + H_2 \rightleftharpoons Ni + 2NH_4^+ + (x-2)NH_3 \quad (115)$$

In practice, x is maintained at about 2.0, and therefore the molar ratio of NH_3 to Ni does not change appreciably during reduction. Various catalysts are used to initiate the reaction, and the nickel nuclei formed thus continue to catalyze the reaction. The rate of reduction is first order with respect to the concentration of nickel ion and independent of the hydrogen pressure.[412] The effect of a change in the ammonia:nickel ratio on the rate of precipitation at 213 °C is shown in Figure 18, together with a line showing the change in the fraction of the total nickel present as the diammine with the ratio. This line was calculated by the use of stability-constant data extrapolated to 213 °C. The similarity of the two lines suggests that the reduction of the diammine species is more rapid than that of other species present; this information is of obvious value in the control and optimization of the reduction process, since it permits the optimum nickel:ammonia ratio under various conditions to be calculated from thermodynamic data. The results for cobalt[413] are similar, the maximum rate being at a cobalt:ammonia ratio of about 2.8:1.

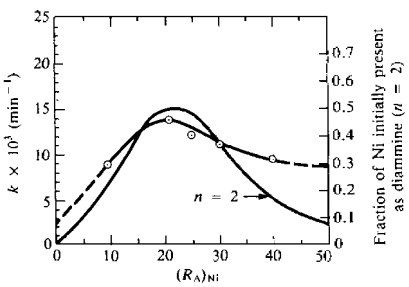


Figure 18 Effect of ammonia to nickel ratio $(R_A)_{Ni}$ on the apparent first-order reaction rate constant k. Also drawn is the line ($n = 2$) showing the fraction of total nickel initially present as $Ni(NH_3)_2^{2+}$ ions (after Needes and Burkin, ref. 412)

Cementation, the process by which a metal is reduced from solution by the dissolution of a less-noble metal, has been used for centuries as a means for extraction of metals from solution, and is probably the oldest of the hydrometallurgical processes. It is also known by other terms such as metal displacement or contract reduction, and is widely used in the recovery of metals such as silver, gold, selenium, cadmium, copper and thallium from solution and the purification of solutions such as those used in the electrowinning of zinc. The electrochemical basis for these reactions has been well established[414] and, as in leaching reactions, comprises the anodic dissolution of the less-noble metal coupled to the cathodic reduction of the more-noble metal on the surface of the corroding metals. Therefore, in the well-known and commercially exploited[44] cementation of copper from sulfate solution by metallic iron, the reactions are

$$Cu^{2+} + 2e^- \longrightarrow Cu \quad (116)$$

$$Fe \longrightarrow Fe^{2+} + 2e^- \quad (117)$$

The coordination chemistry of both metal ions involved plays a vital role in governing the thermodynamics and the kinetics of such reactions. This will be illustrated by reference to the chemistry involved in the precipitation of gold from cyanide leach liquors by metallic zinc powder — the most widely applied method for the recovery of gold from solutions.[415] The overall reaction is

$$2Au(CN)_2^- + Zn \rightleftharpoons 2Au + Zn(CN)_x^{2-x} + (4-x)CN^- \quad (118)$$

where x is dependent on the concentration of free cyanide and, under normal operating conditions, is between 3 and 4. As a result of the exceptional stability of the dicyanoaurate ion, variations in the solution conditions have little influence on the cathodic reduction reaction. On the other hand, hydrolysis of the zinc ion to produce insoluble hydrated oxides is possible under certain conditions of pH and cyanide concentration, as shown in Figure 19. For efficient cementation, which requires the removal of gold to concentration levels below 5×10^{-8} M, it is vitally important for conditions to be maintained that do not allow oxides to form, since passivation of the zinc surface inhibits

and, in some instances, prevents further reaction. For this reason, the concentration of free cyanide is generally maintained above about 4×10^{-3} M, and the solutions are deoxygenated before cementation. The latter operation is essential because the reduction of the dissolved oxygen by the reaction

$$O_2 + 2H_2O + 4e^- \longrightarrow 4OH^- \tag{119}$$

can result in (a) excessive consumption of the zinc, and (b) high concentrations of zinc and hydroxyl ions at the surface, both of which are conducive to the formation of oxides on the surface. Table 7 illustrates the importance of the concentration of free cyanide in the maintenance of efficient extraction even in the absence of oxygen, particularly at higher concentrations of gold.

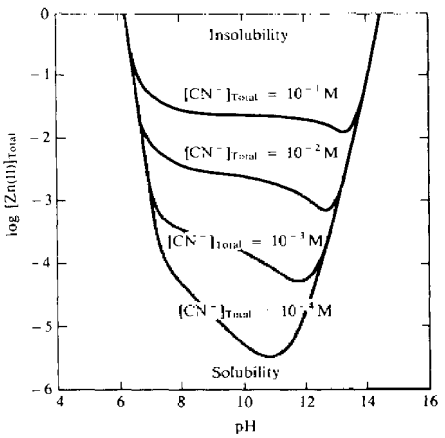


Figure 19 Domains of solubility and insolubility of Zn^{II} in cyanide solutions at 25 °C

Table 7 Effect of Cyanide Concentration on the Cementation of Gold

[Au] (mg l^{-1})	*[NaCN]* (M)	*Rate of cementation* (μg cm^{-2} h^{-1})
0.05	0.001	1.03
0.05	0.002	1.34
0.05	0.005	1.32
5.0	0.001	41.3
5.0	0.005	99.7
5.0	0.010	107

Although gold forms particularly stable cyanide complexes,[16] it is fortunate that the main impurities in the cyanide leach liquors, such as iron, copper, nickel, cobalt and zinc, also form strong complexes with the cyanide ion. Therefore, although the concentration of iron, in the form of ferrocyanide, can be some orders of magnitude greater than that of the gold, the iron does not interfere, owing to the stability of the ferrocyanide ion, which prevents reduction to the metal at the potentials at which the cementation of gold occurs. The same is true of the other major impurity ions. A knowledge of the thermodynamics of the formation of the cyano complexes is therefore of considerable assistance in the prediction and interpretation of the roles of the various ions in the cementation process.

On the other hand, the recovery of some metals (notably those of the platinum group) by cementation is particularly difficult. This applies particularly to their removal from the waste streams of the refineries. In a typical process for platinum-metal refining,[416] the metals are dissolved as their chloro complexes and, although reactions such as

$$PtCl_4^{2-} + 2Fe \rightleftharpoons Pt + 2Fe^{2+}(2Cl^-) \tag{120}$$

are thermodynamically favourable, the well-known[417] kinetic inertness of these complexes results in unacceptably low rates of reduction of all the platinum-group metals (except palladium, which forms complexes that are considerably more labile) by active metals such as iron, aluminum or zinc. This characteristic of the coordination chemistry of these metals also accounts for the difficulty experienced in the devising of suitable methods for their production in the pure metallic form by electrowinning from aqueous solutions.

63.3.5 Electrochemical Processes

The production of pure metals by electrowinning or electrorefining is often the preferred final step in an extractive metallurgical process. A large number of metals are recovered by electrochemical reduction, the most important of which are (in order of quantity produced) aluminum, copper, zinc, magnesium, nickel, manganese, cobalt, chromium, titanium, the precious metals (gold, silver and the platinum-group metals) and the alkali metals. With the exception of aluminum, magnesium, titanium and the alkalis, which are electrowon from fused-salt electrolytes, aqueous solutions are employed for the electrowinning of these metals.

On the basis of their electrochemical behaviour in *aqueous* solutions, the metals can be divided roughly[418] into three main classes, as shown by the portion of the periodic table of the elements reproduced in Table 8. (a) *Normal* metals show reversible behaviour; are deposited with low overpotentials at high current efficiencies to give deposits with well-developed, relatively large grain sizes that are not readily affected by addition agents; and have relatively high overpotentials for hydrogen evolution. (b) *Inert* metals exhibit irreversible behaviour; are deposited with high overpotentials at current efficiencies that are generally lower than 90% (in some cases, lower than 50%) to give fine-grained, stressed deposits that are readily modified by the addition of smoothing agents; and have low overpotentials for hydrogen evolution.

Table 8 Electrochemical Characteristics of the Elements

Li	Be	No deposits									No deposits		B	C	N	O
Na	Mg												Al	Si	P	S
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	
Cs	Ba	R.E.	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	
Normal as amalgams			Inert; no deposits		Inert					Normal					Intermediate	

In general, the practical applications of this classification are apparent when one considers that the electrowinning or refining of the normal metals presents few problems. In contrast, the recovery of the inert metals by electrodeposition is more difficult, the degree of difficulty decreasing from left to right in any row of Table 8, *e.g.* the electrowinning of chromium[419] metal is significantly more difficult than that of nickel,[420] which, in turn, is more difficult than that of copper. These trends are due to thermodynamic as well as kinetic factors, the nobility of the metals tending to increase from left to right, whereas the kinetic factors cannot be correlated as easily with the positions of the metals in the table. However, it has been suggested[421] that the rate of electrochemical reduction of simple aqua ions (as reflected in the exchange current density) can be correlated with the rate constant for the substitution of water in the inner coordination sphere of the ions, as shown by the data in Figure 20. The rate of loss of coordinated water therefore appears to be an important step in the overall reduction and electrocrystallization of metal aqua ions. This is one of the main reasons why the electrowinning of chromium is difficult, in contrast to the relative ease with which zinc is deposited[422] even from acidic solutions, despite the similarity of the thermodynamics of the two reactions.

Hydrolysis of the metal ions to form non-conducting layers of hydrated oxide on the surface of cathodes is one of the most important characteristics of electrowinning of the inert metals, and is one of the most serious problems. The simultaneous evolution of hydrogen during the deposition of these metals results in an increase in pH close to the cathode surface that can (if the solution is not adequately buffered) result in the incorporation of oxide into the deposit and even, in some instances, in the cessation of metal deposition. Partly because of this, sulfate solutions are preferred to, for example, chloride electrolytes, because the buffering action of the sulfate–bisulfate equilibrium reduces the possibility of local high pH values. Therefore chromium of high (> 99%) purity can be electrowon from sulfate solutions,[419] but oxide inclusions in deposits from chloride solutions limit the purity to less than 95%. Furthermore, for manganese the formation of relatively weak

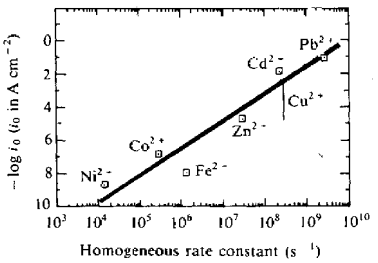


Figure 20 Correlation between the exchange current densities for deposition of divalent metal ions and the corresponding rate constants for substitution of water (after Vijh and Randin, ref. 421)

(K_1 = 10) ammine complexes is crucial to the electrowinning process since it delays the precipitation of manganese hydroxide on the cathode surface until the pH value is above 9, at which stage the buffering action of the ammonia–ammonium ion equilibrium comes into effect.[423] For this reason, the electrowinning of manganese is carried out in solutions containing ammonium sulfate at concentrations above 1 mol dm^{-3}.

The role of coordination chemistry in electrowinning processes is most obvious in the recovery of chromium.[419] In solutions of ammonium sulfate, chromium(III) can be present in a variety of forms, depending on time, temperature and the history of the solution. At higher temperatures, a variety of green sulfato complexes, such as $[Cr(H_2O)_5SO_4]^+$, and $[Cr(H_2O_5)OH]^{2+}$, and olated species, such as $[(SO_4)(H_2O)_4Cr—O—Cr(H_2O)_5]^{2+}$, form as a result of penetration by the sulfate ion, and hydrolysis and polymerization of the simple hexaaqua ion, which predominates in cool, dilute solutions of moderate acidity. This difference is put to good use in the so-called Marietta process, in which iron can be removed selectively from a sulfate leach liquor containing chromium and iron by selective crystallization as an alum after the chromium has been converted to the inert form by heating to 80 °C. However, the electroreduction of these species is significantly slower than that of the hexaaqua ion, and the conditioning of the solution after the removal of the iron must be carried out at lower temperatures (lower than 30 °C) for several days to allow the hexaaqua ion, which precipitates as an alum and is dissolved in the catholyte of the electrowinning cells, to reform.

63.4 PYROMETALLURGY

Slags, which are mainly oxide mixtures, are associated with many of the important processes of ferrous and non-ferrous extractive metallurgy, and an understanding of their behaviour is essential to the control of these processes. Unfortunately, the practical difficulties associated with the study of phases at high (> 1000 °C) temperatures impose severe limitations on the range of techniques suitable for the study of the coordination chemistry involved. As a result, metallurgists have traditionally studied only the macroscopic properties of silicate slags, such as the phase equilibria, thermodynamic activities and transport properties, and only in recent years have attempts been made to adapt spectroscopic techniques, which have proved so useful in studies of solutions at ambient temperature, to high-temperature systems. The coordination chemistry of molten slags is therefore not understood in detail at this stage.

Ceramicists and physicists have studied the structures of silicate glasses and have interpreted the results in terms of characteristics such as the size, polarizability, and coordination number of the ions, whereas metallurgists have employed a less quantitative description in terms of the acidity or basicity of the components constituting the slag.[424]

The many forms of crystalline silica are arrangements of the SiO_4 tetrahedron linked to four others by bridging (—O—) bonds. During melting, the crystalline network is partially destroyed and, as the temperature is increased further, the degree of polymerization (n) in the structure $(Si_nO_{3n+1})^{2(n+1)-}$ decreases gradually. Therefore, the transformation from solid silica to a viscous liquid takes place in several stages in which no well-defined fusion point can be discerned, and the physical properties, such as viscosity and electrical conductivity, also show gradual changes.

In slags consisting mainly of oxides, an acid can be regarded as an acceptor of oxide (O^{2-}) anions, whereas a base is a source of these ions. In the presence of an acid, amphoteric oxides behave as bases, whereas in the presence of a base, they behave as acids. Examples of these are:

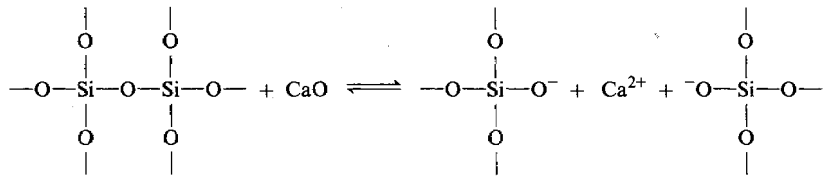
Acid $\quad SiO_2 + 2O^{2-} \rightleftharpoons SiO_4^{4-}$ (121)

Base $\quad CaO \rightleftharpoons Ca^{2+} + O^{2-}$ (122)

Amphoteric $\quad Al_2O_3 + O^{2-} \rightleftharpoons Al_2O_4^{2-}$ (123)

$$Al_2O_3 \rightleftharpoons 2Al^{3+} + 3O^{2-} \quad (124)$$

As can be seen, most slags are silicates and, if a basic oxide is added to the hexagonal network of silica, it introduces O^{2-} ions into the network, partially destroying it:



(125)

A neutral slag is a slag that contains enough O^{2-} ions to ensure that each tetrahedron of the acid oxide is independent of the rest. In the binary system $CaO-SiO_2$, neutrality will be reached at the composition $2CaO \cdot SiO_2$. Therefore, according to whether the mole percentage of SiO_2 is lower than, equal to, or higher than 33%, the slag will be basic, neutral or acidic respectively. The oxides can be classified[424] in terms of their acid–base character, as shown in Table 9.

Table 9 Acid-Base Character of Common Oxides

Oxide	$Z/(R_c + R_a)^2$	*Coordination number of liquid*	*Character of oxide*
Na_2O	0.18	6–8	
CaO	0.15	6–8	Basic – network breakers
MnO	0.42	6–8	
FeO	0.44	6	
ZnO	0.44	6	
MgO	0.48	6	
Cr_2O_3	0.72	4–6	
Fe_2O_3	0.75	4–6	Amphoteric
Al_2O_3	0.83	4–6	
TiO_2	0.93	4	
SiO_2	1.22	4	Acidic – network formers
P_2O_5	1.66	4	

It is of interest that the order parallels that of increasing degree of covalent character of the oxide as approximated by the coulombic term $Z/(R_c + R_a)^2$, where R_c and R_a are the ionic radii. The assignment of the terms 'network formers' and 'breakers' is obvious from the discussion above.

This classification of the oxides in terms of their coordinating properties for oxide anions has been particularly useful in the interpretation of the transport properties of the slags encountered in metallurgical processes, and has considerably simplified the design of suitable slag compositions. In particular, the addition of fluxes to reduce the viscosity of a slag is an important component in the optimization of a slag system. From the above, it should be clear that the addition of a basic (or network-breaking) oxide to an acidic slag such as silica should result in decreased viscosity. In the same way, silica acts as a flux for basic slags. Examples of such effects are given in Figure 21. As could be predicted, the addition of alumina increases the viscosity of a basic slag but decreases that of an acidic slag. The correct choice of the material for the refractory lining of furnaces has also been simplified by the application of the concepts outlined above.

Recent X-ray and Mössbauer studies[425] of silicate slags with compositions similar to those used in the making of iron and steel have revealed that the simplified interpretation of the coordination chemistry of slag systems given above must needs be modified and extended when transition metal ions are involved. This is shown by the Mössbauer spectrum in Figure 22, from which it has been deduced that iron(III) is tetrahedrally and octahedrally coordinated in a typical silicate slag. When this type of information can be determined at high temperatures and for the other important metals (such as chromium, manganese, nickel and cobalt) that are present in pyrometallurgical slags, it will be invaluable as an aid to the advancement of the present understanding of the mechanisms of redox reactions occurring during pyrometallurgical processes.

There are several interesting parallels between the chemistry of aqueous solutions and that of high-temperature systems. This can best be illustrated by a discussion of the chemistry involved in the smelting of base-metal sulfide concentrates, which is the preferred route for the recovery of copper, nickel, cobalt and lead. The first step in such a process is the melting of the concentrate in the presence of additional slag-forming constituents to produce a two-phase system consisting of a matte (or molten sulfide) and a slag (or molten silicate). In principle, this can be likened to a high-temperature solvent-extraction process, the objective of which is the removal of as much

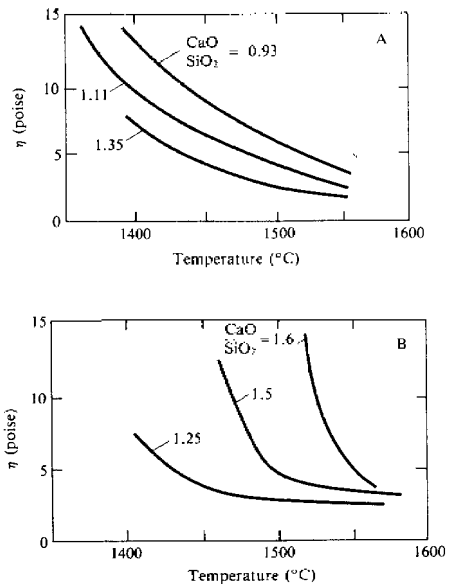


Figure 21 Viscosity of (A) acidic and (B) basic blast furnace slags (after Goudurier, Hopkins and Wilkomirsky, ref. 424)

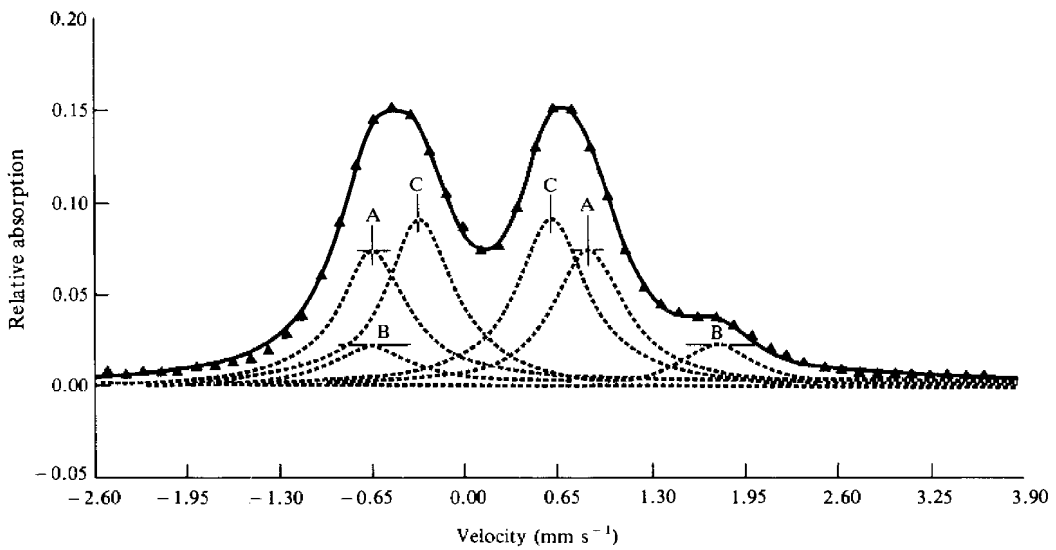


Figure 22 Mössbauer spectrum of a slag containing 25% SiO_2, 31% CaO, 20% Al_2O_3 and 24% Fe_2O_3. The pair A corresponds to Fe_{tet}^{3+}, B to Fe^{2+} and C to Fe_{oct}^{3+} (after Bowker, Lupis and Flinn, ref. 425)

as possible of the impurity metals (such as iron and magnesium) from the sulfide by their extraction into the silicate.

On the basis of the aqueous coordination chemistry of the metal ions involved, the following order of affinity for acceptor ligands such as sulfide ions would be predicted, $Cu^{II} > Ni^{II} > Co^{II} > Fe^{II} > Fe^{III}$, and roughly the reverse order would be expected for ligands such as oxide or hydroxide. This order is retained to a large extent in matte–slag systems, as shown in Table 10, which summarizes some data[426] on the distribution coefficient D_i of species i between the sulfide and silicate phases under oxidizing conditions, calculated on a mole fraction basis.

For copper concentrates, virtually all the iron can be partitioned into the slag by 'blowing', *i.e.* by the introduction of oxygen into the system whereas, for concentrates containing nickel and particularly cobalt, a compromise must be reached between the removal of the iron and the loss of the valuable metals into the slag phase. This is shown by the results[426] in the last two columns of Table 10, which were obtained from a detailed analysis of plant data. An extension of the correlation between the chemistry of aqueous solutions and that of high-temperature melts can be applied to several other important elements that often occur with the base metals. Thus, one would predict a favourable distribution of gold and the platinum-group metals into the sulfide phase and, indeed, the sulfide-rich matte that is formed is a very efficient collector for the precious

Table 10 Distribution of Metals in Smelting Processes

Temperature (°C)	*Element*	D_i	*Recovery* *Matte* (%)	*Slag* (%)
1255	Cu	245	—	—
	Ni	274	—	—
	Co	80	—	—
	Fe	6	—	—
1305	Cu	180	94	3
	Ni	257	87	2
	Co	61	41	44
	Fe	7	0.6	91

metals, which have an average distribution coefficient of about 170.[427] On the other hand, as compared with iron, chromium, which occurs predominantly as chromite, would be expected to favour the slag phase; this is borne out by plant data, which suggest that chromium has a lower distribution coefficient than iron.

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64

Geochemical and Prebiotic Systems

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64.1 INTRODUCTION

> 'Here certainly we are justified in thinking that chemical principles should give us an insight into the ways of nature.'
>
> K. B. Krauskopf[1]

Many diverse processes are involved in the transformation of the elements and their compounds in the Earth. Some of the pathways observed are shown in Figure 1, a version of the so-called 'geochemical cycle'. This cycle is very much simplified and is not a closed one. It may also be 'short-circuited' and indicated processes may be very fast on the geological time scale, or, more often as not, occupy very lengthy periods, amounting in some cases to billions of years.

Although few authors have said so in as many words, coordination compounds and complex ions are at the heart of every stage of the cycle. These include minerals, species in fluids ranging from aqueous solutions to silicate melts, complexes in sediments and asphalts, and chelates intimately involved in life processes and their decomposition products.

This review addresses itself to a description of coordination geochemistry in the geochemical cycle and to related processes in the primitive Earth. We do not pretend that such an immense subject can be exhaustively covered in a short chapter. Rather, attention is given to general concepts, principles and their possible applications. Nor is the list of references by any means exhaustive. However, it does cover the main points and provides an entry to the voluminous literature of the subject. It should be added that many of the possible roles that coordination complexes play in nature are based on speculative interpretations of present day geochemical evidence; such is the nature of many geochemical problems, as many of the reactions are so slow that they do not lend themselves easily to rigorous experimental investigation.

No doubt many discoveries will be made in the field of coordination geochemistry in the near future. This is only to be expected in the light of advances in techniques and instrumentation.

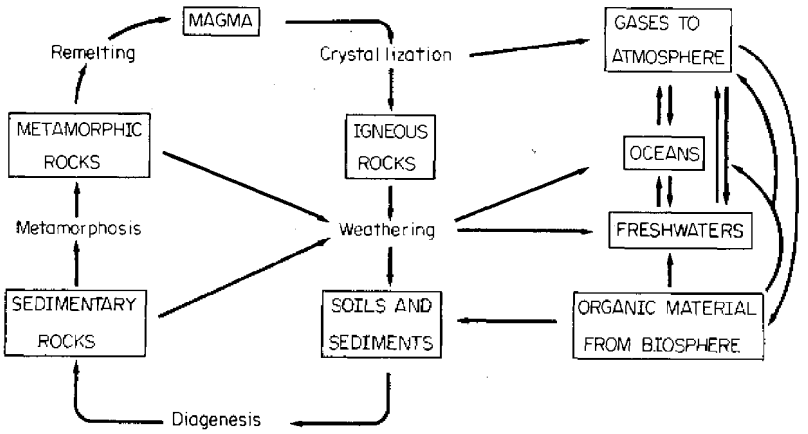


Figure 1 The geochemical cycle

Such findings are to be especially welcome, because without a thorough understanding of the coordination chemistry of inorganic and organic ligands, we cannot begin to understand any of the transformations occurring about us in the natural environment.

64.2 MINERALS

64.2.1 Minerals as Coordination Complexes

Nearly 4000 discrete minerals have been characterized. Except for a few such as the native elements, purely organic species, and simple inorganic substances such as ice, water and carbon dioxide, they are all coordination compounds of one sort or another. It is inappropriate in a review of this size to examine many individual minerals in detail; rather the aim here is to outline the scope of coordination in naturally occurring solid phases. Several excellent compilations of minerals, their compositions, properties and occurrences have been published.[2–7] New and discredited species also appear in lists in *Mineralogical Abstracts*[8] (quarterly) and in the *Mineralogical Magazine*[9] (biannually). The Commission on New Minerals and Mineral Names of the International Mineralogical Association gives approval for each new species gazetted.

In these natural coordination compounds many different donor atoms are involved in bonding to metal ions. Some of these are gathered together in Table 1. Given this ligand set together with all of the combinations afforded by the elements of the periodic table, it is perhaps none too surprising that the number of known minerals is large and that a sizeable number of new ones, perhaps amounting to 100–200, are currently reported each year. The observed diversity is compounded by the many different kinds of structural arrangements possible for the theoretical combinations and by the diversity of new ligands generated by the polymerization of such simple precursor ions as borate and silicate. Fortunately, systematic schemes for the description of polyborates have been proposed[10,11] and the range of ligands constituting the complex silicates has been exhaustively catalogued[12] in the light of the fact that silicate minerals make up the bulk of the Earth's crust. Over the last 50 years or so the advance of X-ray crystallography has allowed a detailed insight into the structures of many minerals. The number of known packing arrangements, the general characteristics of which have been outlined elsewhere,[12–16] is multiplied in the mineral kingdom by the number of isomorphous analogues of species for which single-crystal X-ray studies have been carried out.

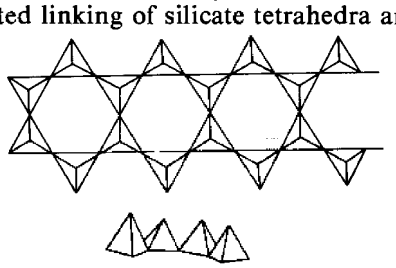
Many simple minerals, especially simple salts like halite, NaCl, sulfides, sulfosalts and oxides, have structures based upon cubic or hexagonal closest-packed arrays of either cations or anions. Coordination geometries of metal ions in many of these kinds of minerals are thus confined to more or less regular octahedra and tetrahedra. The occupancy of the two types of sites is dictated by the stoichiometry of the mineral, the radius of the ions involved and their preferred coordination geometries. Coordination of cations in mineral species in terms of bonding and crystal field effects has been extensively reviewed.[16–21] Comprehensive lists of ionic radii relevant to cation coordination geometries in minerals have also been compiled.[16,21]

Table 1 Some Donor Atoms and Ligands in Minerals

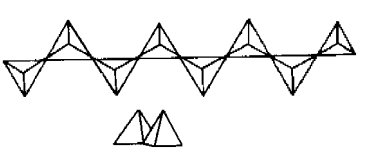
Group	*Donor*	*Ligand types*
IV	C	Carbide, CN^-
	Si	Silicide
V	N	Nitride, organics, SCN^-
	P	Phosphide
	As	Arsenide, diarsenide and mixed anions such as As_2^{2-}, AsS^{2-}
	Sb	Antimonide and arsenic analogues
	Bi	Bismuthinide and arsenic analogues
VI	O	O^{2-}, OH^-, H_2O, borates and polyborates, silicate and polysilicates, borosilicates and aluminosilicates, columbates, tantalates, PO_4^{3-}, AsO_4^{3-}, antimonates, antimonites, arsenites, germanates, germanites, VO_4^{3-}, CrO_4^{2-}, MoO_4^{2-}, WO_4^{2-}, SO_4^{2-}, CO_3^{2-}, NO_3^-, selenate, selenite, tellurate, tellurite, iodate, organic hydroxyl and carboxylate
	S	Sulfide, disulfide and sulfoanions of group V and of Se and Te
	Se	Selenide analogues of S ligands
	Te	Telluride analogues of S ligands, Te_2^-
VII	F	F^- and complex fluorides such as BF_4^-, SiF_6^{2-}, AlF_6^{3-}
	Cl	Cl^- and complex chlorides such as $FeCl_6^{4-}$
	Br	Br^-
	I	I^-

In non-close-packed structures, which indeed account for the bulk of known minerals, higher coordination numbers for cations are frequently encountered. Some specific examples are mentioned in the next section, but it is appropriate here to focus attention briefly on silicate minerals in view of their widespread occurrence and importance as rock-forming minerals. For example, in zircon, $ZrSiO_4$, the Zr^{IV} ion is eight-coordinate as is the Mg^{II} ion in pyrope garnet, $Mg_3Al_2Si_3O_{12}$. A number of cations are present in the amphibole class of silicates with the formula $A_{0-1}B_2Y_5Z_8O_{22}(OH, F, Cl)_2$ (A = Ca, Na, K; B = Ca, Fe^{II}, Mg, Mn^{II}, Li, Na; Y = Al, Cr, Fe, Mg, Mn^{II}, Ti; Z = Al, Si, Ti). In the micas and in leucite, $KAlSi_2O_6$, twelve-coordinate cations are present (K^+ in the latter), and the K^+ cation is nine-coordinate in the common feldspar orthoclase, $KAlSi_3O_8$.

While the general formula of the amphiboles given above seems at first somewhat unwieldy, it is simple to rationalize this structure, and those of the other complex silicates, as consisting of various polymeric groups of SiO_4^{4-} tetrahedra linked in different ways *via* bridging apical oxygen atoms. In a number of silicates these tetrahedra are replaced by those of AlO_4^{5-}, which are generally larger and cause a distortion of the basic framework, and so compositional variations arise because of the extra cations needed in the lattice to ensure electrical neutrality. In the amphiboles, the SiO_4^{4-} tetrahedra are linked by two or three bridging oxygen atoms to give double chains as shown in (1) with the composition $(Si_4O_{11})_n^{6n-}$. The pyroxenes are based on the simple single-chain structure $(SiO_3)_n^{2n-}$ (2), although the chains are kinked as a result of slight rotations of the monomeric units. If each tetrahedral unit shares three corners to form infinite two-dimensional sheets, the basic framework of the mica group results, with the formula $(Si_2O_5)_n^{2n-}$. When all four oxygen atoms in the monomer are involved in bridging, a three-dimensional framework is formed. Several polymorphs with the basic stoichiometry SiO_2 are known. Replacement of the Si ions by Al^{III} and occupation of interstices thus formed by other cations yields the basic structure of the feldspars. Thus the variety of coordination numbers and geometries in an important class of minerals, the silicates, can be viewed as arising from the disposition of the ligand network formed simply by the regular crosslinking of SiO_4^{4-} and AlO_4^{5-} tetrahedra in a restricted number of ways. Examination of the garnet structure indicates that it is derived from a related linking of silicate tetrahedra and MO_4 octahedra where M is Al^{III}, Fe^{III} or Cr^{III}.



(1)



(2)

While such considerations allow the elaboration of many mineral structures, these ideas are comprehensively treated in the main references given above. Particular aspects illustrating the diversity of coordination modes and complexes in minerals of a more specialized kind are set out in the next section.

64.2.2 Specific Mineralogical Examples of Coordination Compounds

The variety of coordination chemistry in minerals is to some extent exemplified by naturally occurring halide species. Indeed, compounds identical to and related to several classic synthetic substances are known. To illustrate this point, attention is first drawn to fluorides and hydroxyfluorides of Al^{III},[2-5] some of which are listed in Table 2 together with related Mn^{II}, Fe^{II}, Fe^{III} and La^{III} minerals of interest. The occurrences of the Al^{III} fluorides in several pegmatites, the most famous being that at Ivigtut, Greenland, have been compiled by Raade and Hang.[31]

Table 2 Selected Complex Halide Minerals of Al^{III}, Fe^{II}, Fe^{III}, La^{III} and Mn^{II}

Mineral	*Composition*	*Ref.*[a]
Cryolite	Na_3AlF_6	22, 23
Elpasolite	K_2NaAlF_6	23
Pachnolite	$NaCaAlF_6 \cdot H_2O$	24
Thomsenolite	$NaCaAlF_6 \cdot H_2O$	24
Weberite	Na_2MgAlF_7	25
Cryolithionite	$Li_3Na_3Al_2F_{12}$	26
Usovite	$Ba_2MgAl_2F_{12}$	—
Gearksutite	$CaAl(F, OH)_5 \cdot H_2O$	—
Prosopite	$CaAl_2(F, OH)_8$	27
Chiolite	$Na_5Al_3F_{14}$	—
Tikhonenkovite	$SrAlF_4OH \cdot H_2O$	28
Ralstonite	$Na_xMg_xAl_{2-x}(F, OH)_6 \cdot H_2O$	—
Gagarinite	$NaCaLnF_6$[b]	29
Rinneite	NaK_3FeCl_6	30
Douglasite	$K_2FeCl_4 \cdot 2H_2O$	—
Erythrosiderite	$K_2FeCl_5 \cdot H_2O$	—
Chlormanganokalite	K_4MnCl_6	—

[a] In general see refs. 2–5. Selected crystallographic and analytical references are given where appropriate.
[b] Ln = lanthanide(III) or Y^{III} ion.

All of these Al^{III}-containing minerals have that ion hexacoordinated, but a variety of structures are known. Cryolite, elpasolite, pachnolite and thomsenolite all contain isolated AlF_6^{3-} octahedra. The other aluminum fluorides and hydroxyfluorides shown in Table 2 have these units, variously substituted by hydroxide ions, linked together by the sharing of corners or edges in a fashion analogous to the linking of SiO_4 and BO_3 units to form the basic frameworks of the silicates and borates. Cryolithionite thus has the garnet structure and in prosopite the octahedra share two edges, with bridging being effected by hydroxyl ions and the free vertices being taken by fluorides. It is worth noting here that the alkali and alkaline earth cations in these minerals sometimes have unusual coordination sphere geometries. Two crystallographically distinct Na^+ sites occur in cryolite, one octahedral and the other a somewhat distorted cubic antiprism. In weberite the two sodium atoms are also found in crystallographically independent sites, but are both octacoordinated. One lies at the centre of a flattened hexagonal bipyramid and the other in a rectangular prismatic polyhedron. Phase equilibria and conditions of formation of many of these species are known,[32,33] especially in the light of their relevance to the refining of aluminum.

Gagarinite, $NaCaLnF_6$, apparently contains isolated LnF_6^{3-} octahedra, but its crystal structure is unknown. Hexachloromanganate(II) and ferrate(II) ions are present in the minerals chlormanganokalite and rinneite, respectively, and iron(II) or iron(III) ions with four and five chloride ions in the coordination sphere are represented by the species douglasite and erythrosiderite. The coordination spheres are completed by water molecules, and these chloro complexes correspond to well-known compounds prepared in the laboratory.[2]

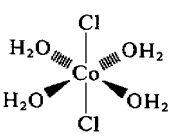
Erythrosiderite, its ammonium analogue, kremersite, and chlormanganokalite are all very deliquescent, a fact in accord with their occurrence around fumaroles and in ejecta at the volcanoes of Vesuvius and Mt. Etna. The former mineral was found associated with molysite, $FeCl_3$, which

is naturally unstable out of this kind of environment. Rinneite has also been reported from Vesuvius.[3] These somewhat bizarre occurrences have also yielded[2] several salts of hexafluorosilicate(VI) and tetrafluoroborate(III). The known minerals of this class are listed in Table 3. Heiratite was first found in a similar volcanic sublimate at Vulcano, and the dimorphs of $(NH_4)_2SiF_6$ have also been reported as sublimates above a burning coal seam at the Bararee colliery at Barari, India. Finally, in this connection, two other simple coordination complexes are known from similar environments at Vesuvius. These are mitscherlichite, $K_2CuCl_4 \cdot 2H_2O$, identical with the artificial salt,[37] and pseudocotunnite, K_2PbCl_4, although this latter species might be $KPbCl_3 \cdot 1/3H_2O$.[3]

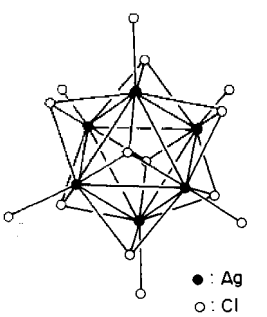
Table 3 Naturally Occurring Hexafluorosilicates and Tetrafluoroborates

Mineral	*Composition*	*Ref.*
Avogadrite	$(K, Cs)BF_4$	2, 34, 35
Ferruccite	$NaBF_4$	2, 35
Hieratite	K_2SiF_6	2, 35, 36
Cryptohalite	$(NH_4)_2SiF_6$	2
Bararite	$(NH_4)_2SiF_6$	2
Malladrite	Na_2SiF_6	2, 34, 35

Three other chlorides which illustrate the range of complexity of this class of minerals, varying from the simplest to the most exotic of stoichiometries, should be mentioned. Albrittonite,[38] $CoCl_2 \cdot 6H_2O$, contains the *trans*-dichlorotetraaquacobalt(II) species (**3**). The same coordination geometry obtains in the analogous unnamed Ni^{II} mineral.[3] Metal cluster complexes are unusual in mineralogy but a notable example is found[39] in the rare oxychloride boléite, $Pb_{26}Cu_{24}Ag_9Cl_{62}(OH)_{47} \cdot H_2O$. In this cubic azure-blue species, six of the silver atoms are arranged in a regular octahedron at the centre of the unit cell. Eight chlorine atoms lie above the faces of this octahedron and six others are positioned normally to the apices as shown in (**4**). This configuration is closely related to those found in such simple synthetic metal cluster compounds as $MoCl_2$ and WCl_2.[40]



(3)



(4)

Two classic pseudohalide coordination complexes are also known to occur naturally. Julienite, $Na_2[Co(NCS)_4] \cdot 8H_2O$, is identical to the well-known synthetic compound[41] and has the thiocyanate ligands bound to the cobalt(II) ion tetrahedrally *via* the nitrogen atoms. The blue complex was originally reported as occurring as needle-shaped crystals in a cobaltian wad from Kantanga, Zaire.[2] The familiar salt $K_4[Fe(CN)_6] \cdot 3H_2O$ is polymorphous and crystallizes in the monoclinic, orthorhombic and tetragonal systems. Square and rectangular plates together with crystals of a monoclinic habit, with a similar formula, have been reported from a number of Soviet gold mines, and have been given the name kefehydrocyanite.[42] However, the single analysis reported indicates that the mineral is a monohydrate. The cyanide ligands were presumably derived from decomposing organic matter and not from leach liquors used in the beneficiation of the ore. Thus, the occurrence is of some significance with respect to the mobilization and enrichment of gold in oxidized ore deposits through the formation of cyano complexes (*vide infra*).

Simple nitrogen-containing ligands are uncommon in mineralogy. A series of species which are derived from or analogous to Millon's base are however known.[43] In these minerals the coordination backbone polymer $[Hg_2N]_n^{n+}$ has large cavities which can be occupied by a variety of anions, and end members can be obtained by ion exchange techniques. Kleinite contains both sulfate

Table 4 Selected Carbonate Minerals

Mineral	*Composition*	*Ref.*
Liebigite	$Ca_2UO_2(CO_3)_3 \cdot 11H_2O$	49
Andersonite	$Na_2CaUO_2(CO_3)_3 \cdot 5\text{-}6H_2O$	50
Grimselite	$K_3NaUO_2(CO_3)_3 \cdot H_2O$	51
Schroekingerite	$NaCa_3UO_2(CO_3)_3(SO_4)F \cdot 10H_2O$	52
Zellerite	$CaUO_2(CO_3)_2 \cdot 5H_2O$	3
Metazellerite	$CaUO_2(CO_3)_2 \cdot 3H_2O$	3
Lanthanite	$La_2(CO_3)_3 \cdot 9H_2O$	53
Calkinsite	$(La, Ce)_2(CO_3)_3 \cdot 4H_2O$	3
Lokkaite	$(Yb, Ca)_2(CO_3)_3 \cdot 1.58H_2O$	54
Ancylite	$(La, Ce)_x(Ca, Sr)_{2-x}(CO_3)_2(OH)_2 \cdot (2-x)H_2O$	55
Burbankite	$(Na, M^{2+}, Ln^{3+})_6(CO_3)_5$	3
Ewaldite	$Ba(Ca_xM_{1-x})(CO_3)_2$	56
Weloganite	$(Sr, Ca)ZrNa_2(CO_3)_6 \cdot 3H_2O$	57
Chalconatrite	$Na_2Cu(CO_3)_2 \cdot 3H_2O$	59
Azurite	$Cu_3(CO_3)_2(OH)_2$	2
Hellyerite	$NiCO_3 \cdot 6H_2O$	60

and chloride ions and has a structure similar to that of high-temperature tridymite.[44] Some non-essential water of crystallization is also incorporated in the channels. Mosesite, prepared by reacting $HgCl_2$ with dilute aqueous ammonia, has the cubic cristobalite structure, space group $F\bar{4}3m$, but natural material contains sulfate, molybdate and carbonate ions together with the essential chloride[45] and is a monohydrate. An anhydrous sulfate analogue, gianellaite, has also been recently reported[46] as has the simple Hg^{II} amidonitrate salt.[47] Some doubt has been cast upon the provenance of this latter mineral, found in an abandoned mine in Colorado, USA, and it may have been formed as a result of the kind of explosives using ammonium nitrate used in the workings. It has also been suggested that the classic coordination compound copper(II) acetate monohydrate, reported[48] as an alteration product of native copper from the Onganja mine, Namibia, may be artificial as well, produced as a result of specimen cleaning. This is reminiscent of the chloroacetate calclactite,[2] $CaCl(C_2H_3O_2) \cdot 5H_2O$, found as an efflorescence on calcareous rocks, fossils and pottery stored in oak museum cases.

With respect to unusual coordination geometries and the preservation of commonly characterized solution species in mineral lattices, together with the occurrence of coordination compounds frequently encountered in the laboratory, several minerals containing oxygen donors ought to be mentioned. A few carbonates are especially noteworthy. These are collected together in Table 4. The four uranyl carbonates liebigite, andersonite, grimselite and schroekingerite have been shown to contain the $UO_2(CO_3)_3^{4-}$ anion, which adopts the expected hexagonal bipyramid geometry. This is also most probably the case[49] in the related minerals bayleyite, $Mg_2UO_2(CO_3)_3 \cdot 18H_2O$, swartzite, $CaMgUO_2(CO_3) \cdot 12H_2O$, and several others. The tris(carbonato) complex is a well-known aqueous species and is thought to be important in the dispersion of uranium in alkaline groundwaters. Similarly, the bis(carbonato) complex, $UO_2(CO_3)_2^{2-}$, is probably preserved in the structures of zellerite and metazellerite. High coordination numbers are also frequently encountered among complexes of the rare earths, zirconium and hafnium. A few relevant minerals are also listed in Table 4.

In lanthanite, each of the two independent rare earth ions is ten-coordinate. Both coordination spheres may be viewed as distorted Archimedean antiprisms whose square faces are replaced by prisms. Only one coordination site for the metal ions is present in ancylite, due to the fact that all the cations are disordered. The geometry about the metals might be described as a distorted hexagonal bipyramid, one of whose apices is replaced by a triangle of oxygen atoms from two of the carbonate ions and one hydroxyl ion. Ewaldite has been described as a barium calcium carbonate, but the calcium site is occupied by a variety of cations, including the rare earths. Here, the cation is six-coordinated with three oxygen atoms from two carbonate ions lying below it. The coordination sphere is completed by three other oxygen atoms from distinct carbonate groups forming an equilateral triangle above the metal ion.

A review of hydroxycarbonates of the lanthanide elements[58] covering much of the earlier literature has appeared. It has been shown that weloganite crystallizes as discrete enantiomorphs in space group $P1$ and exhibits a remarkable variety of coordination geometries in its structure. Carbonate ions and water molecules link the six cations such that the Zr^{IV} ion is nine-coordinate with three oxygen donors each lying above, below, and in the plane with the metal ion. The

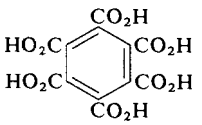
arrangement has but slight distortions from D_{3h} symmetry. The three Sr^{II} ions have independent coordination spheres, but are closely related in spatial terms. The ten oxygen atoms which surround are contained approximately within a hexagonal bipyramid, one of whose apices is replaced by a triangular arrangement of donors. The two sodium ions lie in quite dissimilar environments. Both are six-coordinated, but one has slightly distorted octahedral symmetry and the other lies in the centre of a trigonal prism. This structural extravagance is echoed by many other minerals in the general literature.

A copper(II) complex[59] isolated as a corrosion product from ancient bronze objects has been reported. It is chalconatrite, $Na_2Cu(CO_3)_2 \cdot 3H_2O$, and is identical to the known artificial compound. The origin of its greenish blue colour is due to the solid-state analogue of the very stable coordination complex ion $Cu(CO_3)_2^{2-}(aq)$, which also imparts the characteristic and beautiful colour to the common secondary copper mineral azurite, $Cu_3(CO_3)_2(OH)_2$. Other carbonates of the transition elements are somewhat simpler and hellyerite, for example, contains the ordinary hexaaquanickel(II) ion.[60] Such regular or near-regular octahedral coordination is common in oxides and hydroxides as well as simple aquated metal salts. These include sulfates such as the hexahydrites, $MSO_4 \cdot 6H_2O$ (M = Mg, Zn, Fe, Co) and related species,[61] and somewhat surprisingly, mohrite,[62] the naturally occurring analogue of Mohr's salt, $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$. Hexahydroxo complexes of Sn^{IV} and Ge^{IV},[5,63,64] such as wickmanite and tetrawickmanite, $MnSn(OH)_6$, vismirnovite, $ZnSn(OH)_6$, stottite, $FeGe(OH)_6$, and the unnamed complex $Zn_{0.5}Fe_{0.5}Ge(OH)_6$ and its Mn^{II} analogue, might be thought to belong to this class of minerals as well, although it is unlikely that these species contain the isolated $(Sn, Ge)(OH)_6^{2-}$ ion.

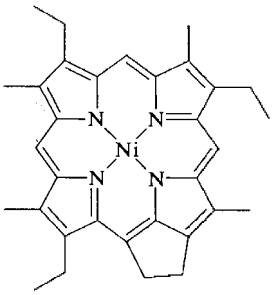
Coordination complexes of organic ligands are widespread in nature, and these are discussed in some detail below. However, but few isolated compounds have been described definitively as mineral species. The same must be said for the many potential organic ligands known to be present in a wide variety of Earth materials. Indeed many of the organic compounds and salts listed in standard reference works[2,3] are ill defined, and a number of them may well be discredited as minerals in the future. Some quite exotic potential ligands are known, including guanine and uric acid (uricite),[65] and phthalimide (kladnoite),[66] but their natural coordination chemistry is largely unknown.

A number of poorly characterized complexes of humic and fulvic acids (*vide infra*) have been reported, such as crenite,[1] the yellow-coloured material in stalactitic calcite crystals from the Harz mountains in Germany. It is probably the calcium salt of a fulvic acid. Similarly, pigotite[2] is an aluminum salt of a related ligand, and volzite is an analogous Zn^{II} complex, but type material was later found[67] to be admixed with wurzite, the high-temperature dimorph of ZnS. Humates in peat, lignites, shales and other sedimentary rocks are invariably complex assemblages of many related ligands. The name sogrenite has been applied[68] to one such mixture containing a considerable quantity of complexed uranyl ion, and a mixed Ca^{II}, Mg^{II}, Al^{III} and Fe^{II} (together with minor amounts of many other elements identified spectrographically) salt of a humic acid, called dopplerite, has been described from a number of localities.[69,70]

Other kinds of coordination compounds involving organic ligands are much better understood. One such class is that of metal complexes of oxalic acid.[2] Calcium oxalate mono- and di-hydrate, whewellite and weddellite respectively, are generally of organic and indeed biogenic origin, but the former has also been noted as a primary mineral in hydrothermal ore deposits. These salts are the main phases present in oxalate-containing human urinary calculi.[71] Another natural coordination backbone polymer is humboltine, the Fe^{II} oxalate $Fe(C_2O_4) \cdot 2H_2O$.[72] Bridging oxalate groups link the Fe^{II} ions in single crystals along the *b* axis to form infinite chains. Other complex oxalates are instantly recognized as coordination compounds. Minguzzite is the potassium salt of the three-bladed propeller tris(oxalato)ferrate(III), $K_3[Fe(C_2O_4)_3] \cdot 3H_2O$.[73] This complex anion is preserved in the sodium magnesium octa- or nona-hydrate mineral stepanovite[74] and the corresponding Al^{III} complex in the same lattice has been given the name zhemchuznikovite. It is appropriate to include two other complexes of oxyacids here, since both are fully characterized. The first is mellite,[75] $Al_2(C_{12}O_{12}) \cdot 18H_2O$, the Al^{III} complex of mellitic acid (**5**). This honey-coloured mineral has been known for nearly two centuries[2] and occurs in a number of European and Soviet lignite deposits. The second is a calcium complex of citric acid[76] identical to the artificial salt $Ca_3(C_6H_5O_7)_2 \cdot 4H_2O$. This complex, earlandite, was found in sediments dredged from the bottom of the Weddell Sea, Antarctica, together with weddellite (*vide supra*). No doubt many other naturally occurring salts of organic acids abound and some of these are mentioned in a later section. However, no others have ever been described as minerals. This is in the most part due to the fact that they are difficult to isolate intact from the bitumens *etc.* in which they occur and



(5)



(6)

that they have not yet been observed as distinct crystals, always being found as complex mixtures with a host of other organic (and perhaps organometallic, in its widest sense) species.

Porphyrins and their complexes are ubiquitous in nature, and are discussed in detail in a later section. Only one, abelsonite, has been accorded a separate mineral name. Found as aggregates of purple plates in drill core from the Green River formation, Utah, USA, it proved to be a Ni^{II} complex[77] with a formula closely approaching $C_{31}H_{32}N_4Ni$. Spectral studies indicated that the mineral was a deoxophylloerythroetioporphyrin based on (6), and was presumably derived from chlorophyll. However, the natural material probably contained water molecules completing the octahedral Ni^{II} coordination sphere. The colours and red fluorescence of quincite, a variety of sepiolite, $Mg_4Si_6O_{15}(OH)_2 \cdot 6H_2O$, from Quincy, France, and of red calcites from Austria, have been ascribed[78,79] to porphyrins or their Ga^{III} and Fe^{III} complexes. More recent work[80] on calcite from Deutsch-Altenburg, Austria, has shown however that the colour in this calcite is due to finely dispersed iron(III) oxides and oxyhydroxides, and the fluorescence to the presence of icosyl alcohol. Other workers[81] have also found that of the several organic components which can be extracted from quincite, none is a porphyrin. The origin of the colour remains unknown.

Limitations of space preclude a comprehensive survey of the coordination chemistry of minerals. The reader is referred to the general references in this section for more information. Naturally, many other examples might have been chosen to exemplify various coordination numbers, geometries and complexes found in minerals. Nevertheless, the various species mentioned above do indicate the wide range of coordination chemistry in the solid state found in the mineral kingdom and the complexity of coordination compounds in the natural environment.

64.3 INORGANIC COMPLEXES IN SOLUTION

It has long been known[82,83] that the formation of coordination complexes plays an important role in the geochemistry of natural aqueous solutions. Application of such reactions to problems concerning the deposition of certain kinds of ores was taken up by Krauskopf.[1,84,85] Many of the applications of complex formation in solution geochemistry and mineral formation were considered in a now classic text by Garrels and Christ.[86] More recently this material has been expanded and built upon by Stumm and Morgan,[87] who also have collected the basic bibliography of the subject. The application of coordination chemistry is central to the understanding of aqueous geochemical cycles and is more far-reaching than might initially be thought. In this section, the coordination complexes of simple inorganic ligands are discussed. However, it should be remembered that species containing organic ligands can be at least as important or even more important in particular instances. This area is dealt with in a later section. Moreover, adsorption phenomena[87] may be viewed in part as coordination processes. Chemical modelling of the distribution of various metals in natural waters as well as analysis of metals associated with particulate matter in such systems indicates that adsorption is sometimes the most significant control with respect to species distributions. Effects have been examined for a number of transition metal ions, lead^{II}, zinc^{II} and cadmium^{II}.[88-91] This area of geochemistry is, however, outside the scope of this review and the interested reader is directed to the above-mentioned work and other references therein. Coordination complexes in silicate melts and gases of natural origin are examined in Section 64.4.

64.3.1 Aqueous Solutions at Low Temperatures

Aqueous coordination complexes in natural systems which involve most of the ligands listed in Table 1, as well as many others, are known. For solutions at around room temperature, the

general chemistry of complex formation is well understood,[92–94] and comprehensive compilations of stability constants for hydrolyzed species and simple inorganic species are available.[95–97] Accordingly, many workers have used this data to examine species distributions of metal ions and complexes in freshwater and seawater. A recent review[98] has tabulated many of the results in terms of periodic trends and lists most of the relevant earlier work in this field.

Table 5 Complexes of Major Dissolved Species in Seawater

Ion	*Significant aqueous complexes*
Ca^{2+}	$CaSO_4^0$, $CaHCO_3^+$, $CaCO_3^0$
Mg^{2+}	$MgSO_4^0$, $MgHCO_3^+$, $MgCO_3^0$
Na^+	$NaSO_4^-$, $NaHCO_3^0$
K^+	KSO_4^-

Table 5 lists the important complex species, aside from free aquated metal ions, of the major ions in seawater, and Table 6 gives similar information for first-row transition and other selected elements which are present in much lower concentrations.[1] Speciation patterns for other elements are listed in an earlier reference.[98] It is clear that only a few types of complexes are formed under these conditions. This is a natural consequence of the concentration and availability of the common ligands (Cl^-, H_2O, OH^-, SO_4^{2-}, CO_3^{2-}) and the low concentrations of most metal ions in natural aqueous solutions. Even for these simple species, however, complex geochemical interactions are indicated. For instance, it has been shown[105] that MOH^+ (M = Cu, Zn) complexes are those species adsorbed on geothite, α-FeOOH, and that MCl^+ (M = Pb, Cu, Zn) species are preferentially adsorbed on the same phase from chloride-containing solutions. Implications arising from such findings for the accumulation of elements in deep-sea manganese nodules and related media are obvious.

Table 6 Complexes of Selected Trace Elements in Freshwater and Seawater

Metal ion	*Significant aqueous complexes*		*Ref.*
	Freshwater[a]	*Seawater*[b]	
Ti^{IV}	$TiO(OH)^+$, $TiO(OH)_2^0$	$TiO(OH)^+$, $TiO(OH)_2^0$	98
V^V	$H_2VO_4^-$, $H_3VO_4^0$	HVO_4^{2-}, $H_2VO_4^-$, $NaHVO_4^-$	98
Cr^{III}	$Cr(OH)_2^+$	$Cr(OH)_2^+$	98, 99
Cr^{VI}	CrO_4^{2-}, $HCrO_4^-$	CrO_4^{2-}, $NaCrO_4^-$, $KCrO_4^-$	98
Mn^{II}	$MnSO_4^0$	$MnCl^+$, $MnCl_2^0$, $MnHCO_3^+$, $MnSO_4^0$	98, 100, 101
Fe^{II}	$FeSO_4^0$	$FeOH^+$, $FeCl^+$, $FeSO_4^0$	98, 102
Fe^{III}	$Fe(OH)_3^0$	$Fe(OH)_3^0$	98
Co^{II}	$CoSO_4^0$	$CoOH^+$, $Co(OH)_2^0$, $CoCO_3^0$, $CoCl^+$, $CoSO_4^0$	98, 103
Ni^{II}	$NiSO_4^0$	As for Co^{II}	98
Cu^I	$CuCl^0$	$CuCl^0$, $CuCl_2^-$	98
Cu^{II}	$CuOH^+$, $CuSO_4^0$, $CuHCO_3^+$, $CuCO_3^0$, $Cu(OH)_2^0$	As for freshwater plus $CuCl^+$, $Cu(CO_3)_2^{2-}$	98, 104
Zn^{II}	$ZnSO_4^0$	$ZnOH^+$, $Zn(OH)_2^0$, $ZnHCO_3^+$, $ZnCO_3^0$, $ZnSO_4^0$, $ZnCl^+$, $ZnCl_2^0$, $ZnCl_3^-$, $ZnCl_4^{2-}$	98, 104
Pb^{II}	$PbOH^+$, $PbCO_3^0$, $PbHCO_3^+$, $PbSO_4^0$	As for freshwater plus $Pb(SO_4)_2^{2-}$, $PbCl_2^0$, $PbCl_3^-$, $PbCl_4^{2-}$	98, 104
Hg^{II}	$HgOH^+$, $Hg(OH)_2^0$, $HgCl^+$, $HgCl_2^0$, $HgCl_3^-$, $HgCl_4^{2-}$	Chloride complexes as for freshwater	98

[a] pH 6. [b] pH 8.2.

The role of the simple inorganic species listed in Table 6 in the formation of orebodies from aqueous solution has been reviewed.[106] Bauxite, copper ores and iron and manganese deposits were examined. Particular attention was paid to coordination complexes in slightly alkaline groundwaters. The coordination chemistry of gold in the natural environment, especially with respect to its migration and enrichment in certain oxidized sulfide orebodies, provides another excellent example of the variety of ligands which may be involved in complexes of geochemical interest. This has been the subject of an excellent recent review[107] and has attracted the attention of geochemists for several decades.[108] Gold has been observed to migrate in groundwaters in the oxide and gossan zones of auriferous sulfide deposits, and to reprecipitate nearer the water table.

Similar behaviour is also displayed by copper and silver, the former being responsible for large economic concentrations of that element particularly associated with weathered porphyry and other ores. Since gold is the most inert of elements, its passage into and transport in aqueous solution must be due to oxidation in the presence of suitable ligands. For many years the chloride complex $AuCl_4^-$, formed in chloride solutions by reaction of gold with, say, $MnO_2(s)$, was thought to be the most likely complex. Recent work however has indicated[107] that $AuBr_4^-$, $Au(CNS)_4^-$, AuI_2, $Au(CN)_2^-$ and $Au(S_2O_3)_2^{3-}$ could all be implicated. The mixed ligand complex $AuClBr^-$, which is one of the main forms of gold in seawater[109] together with $AuCl_2^-$, may also be important. Thiocyanate has a negligible concentration in soils, but cyanide from, for example, decomposing plant glycosides could account for many of the observations. The bis(thiosulfato) complex may prove to be the most important since thiosulfate can be generated as an intermediate in the oxidation of sulfides such as pyrite, FeS_2, themselves in close association with native gold particles.

Excluding brines of various kinds, which are dealt with in the next section, groundwaters may have somewhat different concentrations of inorganic ligands than surface waters and processes involving complex formation and speciation are thus altered. In general, the concentration of dissolved silicic acid, $H_4SiO_4^0$, is higher in these environments and several workers have examined complex formation with it. Major silicate species and complexes present in natural waters are $H_4SiO_4^0$, $H_3SiO_4^-$, $H_2SiO_4^{2-}$, $MgH_2SiO_4^0$, $MgH_3SiO_4^+$ and their Ca^{II} analogues.[98] Other minor species which may have some geochemical significance especially in the formation of deep-sea nodules are $FeH_3SiO_4^{2+}$ and $MH_2SiO_4^-$ ($M = Co^{III}$, Fe^{III}).[110,111] Other complexes involving polymerized silicate and aluminosilicate[112] species may also be important in groundwaters, but little is known of their true significance. The geochemistry of uranium in natural waters has been thoroughly reviewed.[113,114] The species $UO_2HSiO_4^-$ may influence the mobility of the uranyl ion under some circumstances, but the most significant complexes of this cation under most geochemical conditions are $UO_2CO_3^0$, $UO_2(CO_3)_2^{2-}$, $UO_3(CO_3)_3^{4-}$, an extremely stable complex indeed, and one mentioned extensively in the literature, and $UO_2(HPO_4)_2^{2-}$. At low pH and under suitable redox conditions, U^{IV} fluorides can account for significant amounts of uranium present in solution, and U^V species may also be involved. A review of thorium data[115] indicates a number of similarities to uranyl complexes with respect to geochemical behaviour. Inorganic complexes of geochemical interest are $Th(SO_4)_2^0$, ThF_2^{2+}, $Th(HPO_4)_2^0$, $Th(HPO_4)_3^{2-}$ and $Th(OH)_4^0$.

A final example concerns the formation of heteropolynuclear hydroxide complexes.[116] The complexes $[(OH)Fe(OH)_2Cr]^{3+}$, $[(OH)Fe(OH)_2Cr(OH)]^{2+}$ and $[(OH)_2Fe(OH)_2Cr(OH)]^+$, or polymers such as $Fe(OH)_2M_x^{n+}$ ($M = V$, Cr, Mn, Co, Ni, Cu; $n = 2$–4) have been studied with a view to an understanding of the inclusion of transition metals in iron ores as mixed oxides rather than their occurrence as discrete mineral phases. Many other examples might have been chosen in this section. Reference should be made to the general reviews given above. However it should be clear that simple inorganic coordination complexes play a major role in the chemistry of natural aqueous systems at low temperatures.

64.3.2 Coordination Chemistry of Brines

Inorganic coordination chemistry of very saline fluids has received considerable attention with respect to the transport of metals in groundwaters and hydrothermal systems and the emplacement of a number of different kinds of orebodies. Two lines of evidence are of particular importance, and have both been set out in considerable detail in a series of articles by several authors in a recent work.[117] The first of these concerns the nature of fluid inclusions in various ore and gangue minerals from numerous sulfide and oxide ore deposits.[117,118] In general the contents of these inclusions are very saline with chloride molalities up to the order of *ca.* 5 molal and the major balancing cations are Na^+, Ca^{2+}, Mg^{2+} and K^+. Many fluid inclusions also contain high concentrations of CO_2 liquid or gas and varying amounts of other ligating components. These observations provide compelling evidence that metals in many deposits were transported as inorganic complexes. Some inclusions contain significant amounts of base metals.[117–120] Equally as striking as these observations is the occurrence of hot metalliferous brines associated with continental and ocean deeps, and which are comparable in composition to many fluid inclusions.[117] Particular examples occur in the Red Sea area, the Caspian Sea, the Salton Sea, along mid-ocean ridges and in association with continental oil field salt domes and deposits. The classification and role of systems such as this in metal transport have been outlined by White.[121] Other ligands which can also be important in these brines are F^-, Br^-, I^-, NH_3 and sulfur-containing species. A recent provocative review[122] suggests that organic ligands may also be involved in certain brines in the emplacement

of Mississippi-type deposits, but their significance has not been fully assessed. Bubble-filling temperatures of fluid inclusions indicate that many sulfides were deposited at temperatures ranging from about 50 to a few hundred degrees. Sulfides associated with geothermal brines such as pyrite, FeS_2, chalcopyrite, $CuFeS_2$, galena, PbS, and blende, ZnS, provide indisputable evidence that circulating saline waters are intimately involved in mineralizing processes. A more spectacular example in this respect is the Salton Sea geothermal brine from which the somewhat rarer species chalcocite, Cu_2S, bornite, Cu_5FeS_4, tetrahedrite, $(Cu, Fe)_{12}Sb_4S_{13}$, stromeyerite, AgCuS, and native silver among others, have been observed to crystallize.[123] Indeed primary chloride mineral formation has been noted from a few localities.[124,125]

The solubilities of a number of sulfides in aqueous brines have been the subject of much research and a considerable amount of experimental data has accumulated.[117,126] Such data coupled with modelling experiments have led to an appreciation of the inorganic coordination chemistry of many elements in metalliferous brines. Not surprisingly, a number of species of no significance in surface waters are now thought to be important in these conditions. Some of these involving halide, carbonate and ammonia ligands are given in Table 7. Not included are those species listed for seawater in Table 6, to avoid duplication. No doubt many others could be equally as important. The list is not intended to be comprehensive, but to indicate the range of complexes of geochemical interest in this connection. It is also difficult to distinguish between the significance of these species with respect to other complexes known to exist at higher temperatures, and which are discussed in the next section.

Table 7 Additional Selected Inorganic Complexes of Possible Significance in Metalliferous Brines

Metal ion	*Complexes*	*Ref.*
Pb^{II}	$Pb(CO_3)_2^{2-}$, $Pb(HCO_3)_2^0$, $Pb(HCO_3)_3^-$, $Pb_2(CO_3)_2Cl^-$, $Pb(OH)BrCl_2^{2-}$, $Pb(OH)Br_2Cl^{2-}$, $Pb_4(OH)_4Cl_4^0$, $Pb_8(OH)_{12}Cl_4^0$, $NaPbCl_3^0$, $NaPbCl_4^-$, $PbBr^+$, $PbBr_2^0$, $PbNH_3^{2+}$, $Pb(NH_3)_2^{2+}$	122, 127, 128
Ag^I	$AgCl^0$, $AgCl_2^-$, $AgCl_3^{2-}$, $AgCl_4^{3-}$	117, 129
Cu^I	$CuCl_3^{2-}$	130
Cu^{II}	$Cu(NH_3)_x^{2+}$	131
Be^{II}	BeF_4^{2-}	132
Hg^{II}	HgI_4^{2-}	133

Finally, a separate discussion of sulfide complexes is warranted because of their suggested role[117] in metal transport similar to that outlined above. Attention was drawn to such species not only because most economic ore deposits of transition and related metals are of the sulfide type, but because sulfide and its congeners occur in brines as potential ligands and therefore sulfide is transported together with metals in some hydrothermal solutions, and because of the striking association between elements, sulfides and sulfosalts of group V in many ores. Such complexes are naturally of great significance in solutions at higher temperatures. Many of the species implicated are given in Table 8, although recent examinations of several lines of geochemical and geological evidence tend to suggest that Pb^{II} complexes of this sort probably do not reach appreciable concentrations in hydrothermal systems.[117,122,129] Mixed complexes of sulfide and As^{III} or Sb^{III} may contribute to the transport of gold in alkaline sulfur-rich brines. Other sulfur

Table 8 Some Geologically Important Complexes of Aqueous Sulfide Species[116,117,129]

Metal ion	*Complexes*	*Additional ref.*
As^{III}	$HAsS_2^0$, AsS_2^-	—
Sb^{III}	$HSb_2S_4^-$, SbS_2^-, SbS_3^{3-}, SbS_4^{5-}	134
Cu^{II}	$Cu(HS)_3^-$, $Cu(HS)_4^{2-}$, $CuS(HS)_3^{3-}$	135
Ag^I	$AgSH^0$, AgS^-	—
Au^I	$AuHS^0$, $Au(HS)_2^-$, $Au_2S(HS)_2^{2-}$, AuS^-	136
Pb^{II}	$Pb(HS)_2^0$, $Pb(HS)_3^-$, $HPb(HS)_3^0$	—
Zn^{II}	$Zn(HS)_3^-$	—
Cd^{II}	$Cd(HS)_2^0$, $Cd(HS)_3^-$, $Cd(HS)_4^{2-}$	—
Hg^{II}	$Hg(HS)_3^-$, $HgS(HS)_2^{2-}$, $HgS(H_2S)_2^0$, HgS_2^{2-}	—
W^{VI}	$H_{3-n}WS^{1-n}$, $H_{3-n}WS_3^{1-n}$	137
Sn^{IV}	SnS_3^{2-}	—

ligands could provide alternative modes of complexation for many metals. Thiosulfate and polysulfide (S_n^{2-}; $n = 2$–6) ions have been implicated in coordination complexes of Cu^{II}, Cd^{II} and Pb^{II} in a number of sulfide-rich waters. Polyselenide is also present.[138,139] The geochemical application of polysulfide complex formation has been assessed[140] with a view to an explanation of pyritization, gangue mineral formation and wall-rock alteration in base-metal orebodies. Recently, the presence of Cu^{II} and Fe^{II} complexes of a number of reduced sulfur species in a tidal marsh has been reported.[141] Under suitable reducing conditions in such an environment organic thiol and polysulfide ligands may also be formed. These are anticipated to be strongly involved in Cu^{II} speciation in pore waters under such a regime.

64.3.3 Inorganic Complexes in High-temperature Aqueous Solutions

High-temperature aqueous complex formation is of central importance to metal transport and deposition in hydrothermal systems and the like. Not surprisingly, much less data are available for complex formation in comparison to solutions involving complex systems near room temperature, since such mixtures of interest are experimentally much less accessible. Early work in this field was exhaustively reviewed by Helgeson,[142] and more recent summaries of the state of the art have appeared.[117,129] General approaches to prediction of coordination complexes formed and their behaviour have been outlined by these and other authors.[143,144] The work of Helgeson in this field is particularly noteworthy.[145] In general, all of the complexes mentioned in the last two sections and their congeners might be important, although most recent studies[129] indicate that at high temperatures, of the order of 300–500 °C, the chemistry of complex equilibria may be much simplified compared with analogous multicomponent mixtures at low temperatures. It is only fair to indicate, however, that a much larger body of thermodynamic data needs to be accumulated before an adequate model for high-temperature speciation can be advanced.

At very high temperatures, complex formation must only involve inorganic ligands, and only a few simple ones involving H_2S, H_2O, CO_2 and halides are reckoned to have any significance, although sulfates could play a part as well. Accordingly, attention has been focussed upon the coordination chemistry of these donors, particularly on halide and carbonate complexes in view of the fluid inclusion evidence. Besides species tabulated earlier, a number of other complexes have been claimed to be involved in metal transport under these conditions, and are listed for reference in Table 9. It seems clear that $FeCl^+$, $FeCl_2^0$ and $FeOH^+$ are involved in the formation of high-temperature iron deposits. Carbonates, fluorides and chlorides are almost certainly associated with ore-forming fluids in high-temperature environments connected with pegmatites, greisens and skarns. Nevertheless, it must be said that all of these complexes, and no doubt many others, require considerably more research work to be carried out before their proper functions are completely understood under high-temperature geochemical conditions, and they can be incorporated into the speciation models[156,157] necessary for a rigorous description of hydrothermal ore deposition.

Table 9 Possible Complexes of Importance[a] in High-temperature Mineralizing Solutions[117,120]

Ligand	*Complexes*[b]	*Additional ref.*
Cl^-	$FeCl_2^0$, $Au_2Cl_6(HCl)_n$, $LnCl^{2+}$, $CuCl_4^{2-}$, $GaCl_4^-$	146–149
F^-	LnF^{2+}, SnF_6^{2-}, WF_8^{2-}, AsF_5^{2-}, ZnF_4^{2-}, SeF_6^{3-}, ZrF_6^{2-}, NbF_6^{2-}	149–151
CO_3^{2-}	$Ln(CO_3)_4^{5-}$, $Th(CO_3)_5^{6-}$, $UO_2(CO_3)_3^{4-}$ and related species, W^{VI} and Be^{II} carbonates, $Sn(OH)_3CO_3^-$	149, 152–155
SO_4^{2-}	$Ln(SO_4)_2^-$	—
OH^-	$Sb(OH)_3^0$, $Sb(OH)_4^-$, $Sn(OH)_6^{2-}$	—

[a] In addition to complexes listed in previous tables.
[b] Ln = rare earths.

64.4 GASEOUS TRANSPORT AND SILICATE MELTS

By comparison with studies of complex formation in aqueous solution, the gaseous transport of coordination compounds in geochemical systems has received scant attention despite many pointers to the possibility, especially concerning volcanic emanations, arising from metallurgical processes. In Section 64.2 reference was made to a number of halides associated with fumarolic

activity at Vesuvius, Mt. Etna and Vulcano, Italy. Molysite, the very hygroscopic Fe^{III} chloride, was presumably transported as the dimer Fe_2Cl_6 in the gas phase and a number of other halides, aside from the hexafluorosilicates and tetrafluoroborates transported as gaseous SiF_4 and BF_3, have been noted from the Italian deposits.[2] These include the copper(II) minerals eriochalcite, $CuCl_2 \cdot 2H_2O$, melanothallite, CuCl(OH) (?), hydrocyanite, $CuSO_4$, and dolerophane, Cu_2OSO_4. Gaseous SO_3 is thought to contribute to the latter two species. Other simple halides known to have been transported in the gas phase are chloraluminite, $AlCl_3 \cdot 6H_2O$ (the Al_2Cl_6 dimer possibly being important at higher temperatures), lawrencite, $FeCl_2$, scacchite, $MnCl_2$, chlormagnesite, $MgCl_2$ and cotunnite, $PbCl_2$.

The transport of copper and lead in the vapour phase under such volcanic conditions is well documented. While the Cu_3Cl_3 trimer might be important for the former, abundant evidence for CuCl(g) has accrued. It has been observed spectrographically in volcanic flames at Kilaue,[158] and in high-temperature volcanic gases by other workers.[159,160] The sublimation of CuCl from lavas leading to the crystallization of primary atacamite, $Cu_3(OH)_3Cl$, upon condensation has also been reported.[161] Zinc may also be transported as the volatile chloride under the same conditions and has been noted in fumarolic emissions from the Showashinzan volcano, Japan.[162]

Several workers have speculated on the role that gaseous complexes might play in hydrothermal ore disposition under supercritical conditions or in high-temperature environments where water is absent. Early suggestions were summarized by Shcherbina,[151] who considered that SiF_4, BF_3, $TiCl_4$, $FeCl_3$, $ZrCl_4$, $BeCl_2$, $TaCl_5$, TaF_5 and NbF_6, among simple halides, could all be involved in mineral formation from the gas phase at high temperatures. Other volatile oxyhalides such as $NbOCl_3$, $MoOCl_4$ and $ReOCl_4$ were also considered. More recent work has focussed on the transport of tin[163] as volatile $SnCl_4$, rather than SnF_4, in the formation of cassiterite (SnO_2) deposits. General studies of high-temperature gas-phase metal transport with applications to geochemical processes of ore formation have been reported.[164] Particular emphasis was placed on reactions of base metals and their common ore minerals but it is fair to say that the implications for geochemistry of gaseous complex formation are as yet imperfectly explored.

The coordination chemistry of silicate and aluminosilicate melts is a particularly important subject in view of magmatic processes involved not only with ore genesis, but the much wider subject of the geochemistry of rock-forming processes in magmas of various sorts. The structures of such melts are reasonably well understood at least qualitatively in terms of linking of silicate and aluminate tetrahedra but the general approach has been of a theoretical rather than an experimental nature. Generally, it is thought that melts have structures analogous to those found in silicate minerals and much is owed to studies involving glasses, particularly those using vibrational spectroscopic techniques. It is a fact that silicate melts are highly polymerized and this in turn is reflected by the high viscosity of such systems. A recent series of reviews[165] has placed many studies concerned with this phenomenon, and associated coordination chemistry, in perspective. Application of certain aspects of polymer theory indicates that species such as SiO_4^{4-}, $Si_2O_7^{6-}$, $Si_3O_{10}^{8-}$ and $Si_4O_{13}^{10-}$ are important, together with others. Among these are the metasilicate rings $Si_3O_9^{6-}$ and $Si_4O_{12}^{8-}$, which can polymerize in very siliceous melts to give cylindrical structures. This fact is reminiscent of the beryl structure. The silicon atom is always tetrahedrally coordinated. Aluminosilicate melts have much more complex structures, and the aluminum ion may be four-, five-, or six-coordinated. A considerable controversy has accompanied studies on these systems and a recent excellent review[166] has gathered much of the evidence and results concerning them. Central to our present understanding of melts are the concepts of 'network-forming' and 'network-modifying' constituents.[168,169] Aluminum and silicon, together with accessory phosphorus, belong to the former category and produce melts and glasses with a high degree of polymerization. On the other hand, the 'network modifiers', metallic cations usually, disrupt the basic structures and lower the viscosity of the melts.

Concerning cation coordination in silicate melts, most work in the past has concentrated on partitioning of elements between the melt and various numbers of silicates in equilibrium with it. Burns[18] has analyzed these phenomena in detail in terms of crystal field stabilization energies pertaining to the solid phases. However, only a few studies on coordination sites in the melt have been reported and much of our knowledge of these systems is based on theoretical consideration of potential geometries developed in random rigid-sphere assemblies.

The most important contribution in this area arises from the work of Bernal,[170] which was extended in a general way to mineral structures by Whittaker.[141] It can be shown that in a random assemblage of spheres the average coordination number is lower (typically eight or nine) than that in a close-packed array (12). Of relevance to the considerations of coordination geometry here is the kind of holes generated in these assemblages and their geometry. It was shown that

tetrahedral and half-octahedral holes amounted to some 90% of the resulting sites. Smaller numbers of trigonal prisms, Archimedean antiprisms and tetragonally distorted dodecahedra are also present. These results, as mentioned below, do not fit exactly the experimental picture, as far as it is known, of cation coordination geometries in melts, but they do point to the fact that lower coordination numbers are preferred. This simple notion does fit with a number of experimental observations.

In silicate melts approximating the olivine, $(Fe, Mg)_2SiO_4$, stoichiometry, Ni^{II} is both tetrahedrally and octahedrally coordinated.[172] The disposition of coordination geometry is dependent upon the temperature of the melt as well as on its composition. Higher temperatures favour tetrahedral coordination as does, for example, changing the composition of nickel-containing glasses from those containing low molecular weight alkali metals to those containing potassium or rubidium. It should be pointed out here, however, that reservations need to be placed on the drawing of analogies from glasses to melts. Recent spectral studies show that appreciable coordination geometry changes accompany glass solidification even if quenching is quickly carried out.[173] It is difficult, as well, to attempt to rationalize melt coordination chemistry in terms of only one kind of coordination site for a given element and for a given geometry. Studies involving Ni^{II} in melts of the composition of the pyroxene diopside, $CaMgSi_2O_6$, indicate that at least two octahedral complexes must be present in order to explain electrochemical behaviour.[174] Similar results were found for Co^{II} and Zn^{II} under the same conditions.

The coordination chemistry of iron in such melts is a little better understood. Fe^{III} and Fe^{II} can act as network formers and modifiers in both tetrahedral and octahedral coordination geometries.[175,176] It is also of interest to note in the light of the above results on Ni^{II} that multiple site occupancy is also indicated for Fe^{III}.[177] In a number of CaO-Al_2O_3-SiO_2-FeO glasses two different tetrahedral complexes of this ion can be observed using Mössbauer spectroscopy.

Speciation studies[176] in Na_2O-SiO_2-FeO melts indicate that specific Fe^{III} anionic units are formed which involve $Si_2O_5^{2-}$ ligands. This result, implying an alternative view of metal speciation in silicate melts, is a significant one. It implies that discrete species, which may lend themselves to modelling studies, are important, as opposed to the view of the coordination chemistry of melts being concerned with holes or sites in silicate liquids varying with changing composition. A particularly striking observation in this respect concerns a study of Mn^{III} in sodium silicate melts.[178] Analyses of electronic absorption and luminescence spectra indicated that Mn^{III} was present as a discrete complex and thus that the ion could not be viewed strictly as a network modifier. The consequences of this finding for crystal field interpretations of the crystallization of such ions from silicate melts were outlined. However, the paucity of detailed experimental data in these kinds of systems at the present time makes it difficult to assess the true role of individual coordination complexes in siliceous melts. This is an active field, nonetheless, and it is anticipated that a considerable understanding of this branch of coordination chemistry might be achieved in the next few years.

64.5 COORDINATION GEOCHEMISTRY OF COMPLEXES OF ORGANIC LIGANDS

As has been noted in a previous section, only a few complexes of organic ligands have been characterized as discrete mineral species. This fact is, however, quite out of proportion with respect to the importance of metal-organic interactions in the natural environment. Of course, many complexes formed are quite ephemeral in nature, and metabolic and ultimately diagenetic processes lead to their destruction as the material proceeds further in the geochemical cycle. Nevertheless, many species are robust enough to survive quite drastic treatment and they persist in geological units of great age. It is quite reasonable also to suggest that many more coordination complexes of organic ligands exist in waters, sediments and rocks, including fossil fuel materials, than have been isolated and characterized. This is in no small part due to the fact that they are frequently denatured during the experimental procedures adopted to isolate the organic molecular constituents.

The association of metals with organic fractions of sediments and rocks of various types has long been appreciated.[1] Data have been tabulated and reviewed for shales and other sedimentary rocks,[179,180] coals,[181] asphalts,[182] petroleum[183,184] and humus soils.[185] An excellent review of much of this work and its setting in terms of organic coordination geochemistry is available,[186] and covers most of the early work in this field. Some elemental associations are striking, particularly the occurrence of high concentrations of Ni and V in petroleum and Ga, Ge and U in coals and peats. A major fraction of the metal contained in these materials is complexed to organic ligands.

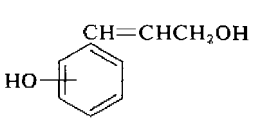
Oxygen and nitrogen donors are probably the most important in this respect, although S, P and As ligands might also play a part. Naturally occurring organometallic compounds, including carbonyls, have received little attention and their significance is barely understood. As well as in these kinds of environments, metal complexation by organic ligands, particularly high molecular weight ones, in natural waters is of crucial importance in the geochemical cycle.[187,188] In the next few sections the coordination geochemistry of such complexes and its significance is discussed. Divisions have been drawn between the various classes of important ligands known to be involved in such processes, although some overlap is found to occur, especially for the so-called 'humic' and 'fulvic' acids. Finally the potential importance of organic coordination complexes in ore deposition is assessed. Environmental coordination chemistry of ligands derived from mankind's activities is not considered here, although the interested reader is directed towards a number of papers presented at a recent conference on this topic.[189]

64.5.1 Complexes of Humic and Fulvic Acids

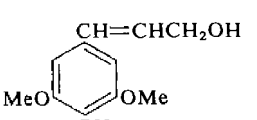
Humic materials of one sort or another represent the vast bulk of the organic material containing reduced carbon in the Earth's crust and in natural waters. They occur in rather more condensed forms in coals, lignites, *etc.*, but much material in sediments and waters, including interstitial pore waters, can be extracted into solution and has a molecular weight range of perhaps 2000 to 300 000. The nature and importance of humic substances has been the subject of a recent authoritative review.[190] The role and importance of coordination complex formation with these materials in the natural environment cannot be overstated, and has been discussed in detail for natural waters,[188,191-193] sediments[194,195] and various sedimentary rocks and coals.[196] In spite of this impressive body of knowledge, however, and the fundamental importance of these complexes in the transport and deposition of many metallic species, our understanding at the molecular level of the kinds of complexes formed is at best sketchy.

This rather unsatisfactory state is partly due to the way in which soluble humic materials are isolated and, somewhat arbitrarily, classified. After extraction of low molecular weight components such as amino acids, fats and so on from soils or sediments or the collection of high molecular weight polyaromatic materials on ion exchange resins, the resulting brown-pigmented polymers are treated with dilute acids and alkali. Extraction of these humic substances with alkali leaves a residue called humin, which itself displays many of the coordinating properties discussed below. The supernatant is acidified, with HCl usually, and the isolated precipitate is humic acid. The yellow and light brown compounds remaining in the filtrate are fulvic acids. Obviously these materials are really complex mixtures of many macromolecules and their structural complexity is compounded by the fact that the origin of these acids is the woody and grassy tissues of plants. Given that there are many thousands of different species alive at present, and indeed many more in the past, this finding is not surprising. Nevertheless, a number of studies have pointed out the main kinds of ligands and chelating groups in humic and fulvic acids and the general kinds of complexes formed are fairly well understood.

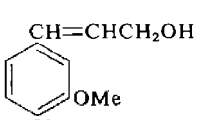
Classically, humic and fulvic acids have been thought of as modified lignins,[197] a view that is strengthened by the fact that they display similar properties to oxidized lignins. Lignin itself has a complex polyphenol-type structure made up of phenylpropane derivatives, including coumaryl (**7**), coniferyl (**8**) and sinapyl alcohols (**9**) and their congeners. These are linked through condensations and dehydrogenations and are substituted by other aliphatic, hydroxyl and alkoxyl groups linked together *via* ether or carbon–carbon bonds. Oxidation of terminal chains would produce carboxylic acid groups, and dealkylation and oxidation would result in phenolic and catecholic (**10**) compounds together with *o*- and *p*-quinone groups; these are generally known to be the major ligating functions in humic and fulvic acids, although, in such complex compounds, other donors are no doubt present, some of which are discussed below.[198] Further degradation in soils and sediments of lignin probably gives rise to the mixtures of benzoic acid, hydroxybenzoic acids, vanillic acid (**11**), quinones, *etc.* which may be extracted from such materials.



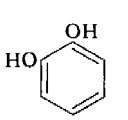
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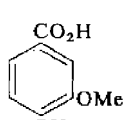
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(9)



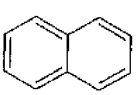
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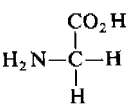
(11)

As a general model of humic and fulvic acid structures the above model explains, in simple terms, the complexation of metal ions in many environments. Functionally, localization of metal ions at carboxylate sites of similar acid strength indicates that these ligands might be viewed in the same light as synthetic crosslinked polyaromatic carboxylic acids.[199,200] Investigations of the role played by quinone groups also indicate that they make major contributions to the metal chelation capacities of humic and fulvic acids.[201] This conclusion was borne out by IR studies and synthetic work on model systems involving benzoquinone. The accumulation of uranium, germanium and vanadium in peats, lignites and other related substances has been suggested to particularly involve the phenylpropane units of lignin.[202] These metals are believed to be incorporated most intensively during early stages of decomposition. Later, as the material reacts and condenses to form humic and fulvic acids, complex stabilities are further enhanced. Furthermore, degradation of humic and fulvic materials from natural waters gives mixtures of polyphenols and phenolic acids[203] and this finding emphasizes that the macromolecular ligands consist of ester- and ether-linked aromatic acids. Similar results are found for soil humic substances.[198]

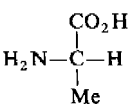
More recent work on fairly well-characterised fulvic acids indicate that these again are polymers of carboxylic–phenolic acids containing both benzene and naphthalene (**12**) nuclei. More revealingly, a high resolution ^{13}C NMR study[205] of freshwater humic substances has apparently identified resonances arising from carboxyl, aromatic, alkyl and alkoxy groups. In the particular humic acid isolated, 40% of the carbon atoms were incorporated in aromatic rings and 24% were present in carboxylic groups. Notwithstanding the consistency of all of these findings, the nature and variety of humic and fulvic acids is in fact even more complicated. It is known[193] that humic and fulvic acids contain nitrogen, sulfur and phosphorus ligands, and the origin of the substances is now thought to arise from the decomposition of all plant components into simple molecules, followed by polymerization with amino acids, sugars and tannins.[191,206] This is in accord with the fact that humic acids can be derived from algae, lichens and mosses. These species do not contain lignin. Flavones, stilbenes, tannins and other phenolic metabolites of microorganisms are all known to be incorporated in some humic acids. Up to 10% by weight of humic and fulvic acids has been shown to be made up of amino acids. The most abundant of these are glycine (**13**), alanine (**14**) and aspartic acid (**15**), although many others have been reported to be present. Naturally, these units can participate in metal complexation in the normal way *via* the formation of stable chelates containing five- and six-membered rings. Monomeric silicic acid or perhaps organically bound silicic acid groups are also frequently found in humic and fulvic acids but their role in bonding is not fully understood. A general reaction scheme[206] for the polymerization of amino acids with phenolic acids to form humic substances is shown in Scheme 1. Condensations of monosaccharides and amino acids *via* the Maillard reaction, followed by dehydration or polymerization, gives rise to brown nitrogenous polymers called melanoidins with very similar composition and spectral properties to other soil humic materials.[207] Other groups known to be incorporated in humic and fulvic acids are various nitrogenous bases and fatty acids.[190] In summary, an entirely satisfactory scheme for the synthesis of humic and fulvic acids is not yet available. Detailed structures are poorly understood. However, the general ligating groups are known, and these are principally carboxyl and phenolic oxygen and amino acid nitrogen atoms. The mixture of molecular structures is complex and may involve other kinds of ligands, including porphyrins.[208,209] In addition the physical form of the humic and fulvic acid can be of importance in the natural environment. Attention has been drawn[189,210] to the presence of composite clay-humic acid particles in the natural environment. Other workers[91,211,212] have studied their effects on trace metal distributions in the marine environment. The organic coatings substantially control the complexation of Cd, Cu and Pb on particles. This work has been extended to a study of Cu^{II} and Ag^{I} uptake by amorphous iron oxides. It was concluded that rather than reactions with simple metal oxide sites, trace element uptake in the natural environment by such substances is probably controlled by their coatings of humic and/or fulvic acids followed by incorporation in the mineral lattice or on *its* surface. However, the chemistry of complex formation is for all intents and purposes the same as that for 'free' humic and fulvic acids, and we make no distinction between these systems here.



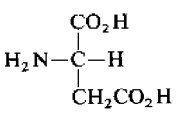
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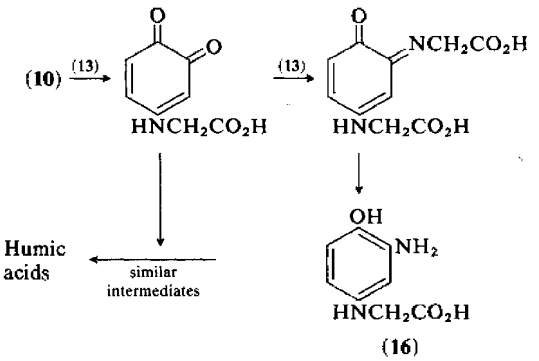
(13)



(14)



(15)



Scheme 1

Many studies have been carried out concerning the stability constants of humic and fulvic acid complexes.[188,190,191] Stability constants vary considerably with pH and ionic strength[213] and this, together with the variable nature of the ligands involved, accounts for the range of values reported for individual metal ions in the literature. However, the stabilities of divalent metal complexes generally follow the well-known Irving–Williams order $Mg < Ca < Mn < Co < Zn \approx Ni < Cu < Hg$.

$$M^{2+} + HA \rightleftharpoons MA + 2H^{+} \quad (1)$$

Table 10 shows some representative ranges of log K values for reaction (1). It should also be noted that humic materials of differing origins have different stability complex behaviour. Soil fulvic acid in general forms the weakest complexes and marine sedimentary humic acid the strongest. Some of the variations can be ascribed to different modes of binding to the humic and fulvic acids. For example Mn^{II}, which does not bind strongly, has been observed to retain a high degree of ionicity.[209] Other workers have shown[214,215] that the $Mn(H_2O)_6^{2+}$ ion appears to retain its inner hydration sphere to a significant degree in Mn^{II}–humic and –fulvic acid aggregates of soil and aqueous origin. Adsorption and binding of this ion, particularly by electrostatic forces, is probably important in complexes of this type.

Table 10 Ranges of Stability Constants[a] for Humic and Fulvic Acids of Various Origins with Selected Metal Ions[188]

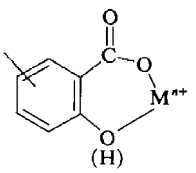
Metal ion	$log_{10}K$
Mg^{II}	3.2–4.1
Ca^{II}	3.2–4.7
Cd^{II}	4.6–5.0
Mn^{II}	4.3–4.9
Co^{II}	4.3–5.0
Zn^{II}	4.8–5.9
Ni^{II}	5.0–5.5
Cu^{II}	7.8–10.4
Hg^{II}	18.3–21.1

[a] Ionic strength = 0.02 molal, pH = 8.0.

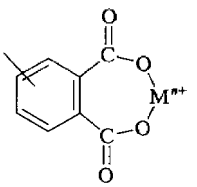
More detailed studies on the nature of complex formation between humic materials and certain individual metal ions have been carried out and it is appropriate to consider these more fully. Fe^{III} and Al^{III} form very strong complexes with fulvic and humic acids and compete for the ligating phenolic and carboxylic groups.[216] This was anticipated by the earlier work of Juste.[217] Similar changes in the IR spectrum were observed upon treatment of a humic acid with Fe^{III} or Al^{III}. Carboxylic groups were considered to be involved in coordination because substantially the same spectral pattern was obtained on treatment of the sample with strong base. On this basis the strong correlations between Fe^{III}, Al^{III} and dissolved organic matter in natural waters is readily understood.[218,219] A series of elegant experiments[220] using ESR and Mössbauer spectroscopy has also shown that more than one complexing site exists for Fe^{III} in humic materials. The first contains the metal ion in a site with tetrahedral or octahedral coordination geometry and binds the metal strongly. The metal ion is resistant to removal by complexation, reduction and substitution

by other metal ions. The second site was associated with the surface of the humic acid ligands. The iron is octahedrally coordinated, more weakly bound and can be reduced and complexed relatively easily. This observation parallels those of other workers,[221,222] who studied the reduction of Fe^{III} to Fe^{II} by humic substances and in model complexes. Fe^{II} is found in considerable amounts as humates even in well-oxygenated waters. This is due to the fact that Fe^{II}–humic acid complexes are quite stable as well as to the ability of humic materials to reduce Fe^{III} to Fe^{II}. Other ligating groups may also be important for Fe^{III}. For example, Mössbauer studies have also indicated[223] that Fe^{III} is associated in part with silicate groups in some humic and fulvic acids.

Copper, lead, cadmium, zinc and probably other divalent transition metal ions appear to compete for similar coordination sites in humic and fulvic acids. However, in a fashion analogous to the case with Fe^{III} some workers have identified more than one site for a particular ion. At least three have been suggested as being available in humic acids for Zn^{II}.[224] Pb^{II} forms complexes with humic acids which are about as stable as Cu^{II} species, but Pb^{II} humates and fulvates are less soluble and quickly coagulate and precipitate.[225,226] This simple fact is of some significance with respect to Pb^{II} distributions in surface water and sediments. The extremely low concentrations of lead in natural waters may partly be explained by the scavenging of lead from solution by such precipitated complexes, *via* adsorption processes or complexation at sites still unoccupied by other metal ions. Several workers have proposed models for the coordination sites responsible for complexation. It has been widely held[227,228] that the interaction of Cu^{II}, Cd^{II}, Zn^{II} and Pb^{II} with fulvic and humic acids involves a salicylic acid group (**17**), but later workers[229] believe that a phthalic acid group (**18**) is involved. No doubt, in actual fact, both kinds of interaction exist in the natural environment together with others mentioned above.



(**17**)



(**18**)

The enrichment of uranium in organic geological units is a well-known phenomenon, and may be sufficient under certain conditions to concentrate enough of the element to make its recovery economic. Szalay[196] has summarized much of the early work in this field and he considers that the formation of polycarboxylate complexes involving humic acids is the overwhelmingly important chemical process in the enrichment. Quite spectacular enrichments are observed, of the order of 10 000:1 in natural water at pH 5–6. Uranium is thought to be present in these complexes as the uranyl, UO_2^{2+}, ion, and uranyl fulvates have been suggested to play a significant role in uranium mobilization in near-surface groundwaters.[230] Subsequent diagenesis of uranium fulvates, humates and humins is expected to lead under reducing conditions to the crystallization of uraninite and pitchblende, $U_{1-x}O_2$. Many deposits of UO_2 are known in which the uranium minerals are associated with high molecular weight carbonaceous matter, graphite and other highly altered organic material. It is generally assumed that this material is probably the remnants of organic substances originally responsible for uranium scavenging from aqueous solution by complex formation.

Considerable attention has also been paid to humic and fulvic acid complexes of vanadium. This is due to the observation of the unusual concentration of this element in a number of bioliths.[231] Enrichment factors of at least 50 000:1 are typical. Vanadium is thought to migrate in water as VO_2^+, VO_3^- and other V^V species,[196] and to be reduced by the humic or fulvic acid to VO^{2+} prior to incorporation into very stable coordination complexes. It has been shown[232] by the application of ESR measurements that the semiquinone groups present in humates are not responsible for the reduction. ESR measurements also lend themselves to the characterization of the V^{IV} humic complexes, and have been employed by a number of workers.[209,215,233,234] All these workers agree that the VO^{2+} ion enters rigid surface sites involving oxygen donors and that it loses rotational mobility, although some nitrogen ligands may also be involved.[234] As opposed to this view, Templeton and Chasteen[233] have shown that model complexes of VO^{2+} with phthalic and salicylic acids give ESR spectra apparently identical to those of VO^{2+}–fulvic acid complexes. There thus seems no real doubt that the usual aromatic carboxyl and phenolic oxygen donors are responsible for complex formation in this case. Szalay[196] also suggested that a similar reduction of MoO_4^{2-} to Mo^V species resulted in molybdenum complexes of humic acids and the accumulation of this element. Other works seems to bear this out,[235] but such processes do not appear to be

involved in the incorporation of tungsten into coals.[236] In this latter instance, it is suggested that complex formation involves the oxygen donor groups of humic and fulvic materials interacting with various cationic hydroxytungstate(VI) species in aqueous solution.

A few other metal-humic acid associations are worth noting. It is possible that Pd^{II} occurs as organic complexes of this type,[237] and Ag^{I} complexes are well known,[238] being formed by linkage to the humic material over the same pH range as the dissociation of the carboxyl and phenol groups occurs. K^+, Ca^{2+} and Al^{3+} all decrease the extent of complexation with Ag^{I}, and, as expected, this effect is more pronounced with the more highly charged cations. Gold may also be mobilized in soil litter horizons and transported as humate complexes.[239,240] However, it is possibly more significant that gold sols are protected by humic and fulvic acids, thus allowing some transport under the right conditions. Inorganic gold complexes with oxidation states I and III, some involving ligands like CN^- and SCN^- derived from decomposing plant material, and which are important in gold coordination geochemistry, are discussed in an earlier section.

Some intriguing variations in the nature of the humate ligands have also recently come to light. Studies of metal fixation in sedimentary organic matter recently deposited in the form of algal mats have been carried out.[241,242] The material was originally derived from cyanobacteria and the humic substances are characterized by a very low aromatic content balanced by the incorporation of large amounts of carbohydrates and amino acids. Similarities between cation coordination *versus* pH curves in titration experiments for UO_2^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Pb^{2+} and Cu^{2+} pointed to a common first step in the complexation of all cationic species. This was suggested to involve bond formation between the metal ion and anionic carboxylate groups. A marked selectivity was also observed. Molybdate, vanadate and germanate were only weakly bound.

Mixed ligand complexes may also exert a significant influence on metal speciation and concentration in natural waters. Fulvate–phosphate complexes of Cu^{II}, Pb^{II}, Cd^{II} and Zn^{II} are more stable than the metal–fulvic acid complexes.[229,243] Incorporation of these species into models in order to estimate free metal ion concentrations gave estimates which were in excellent agreement with concentrations determined experimentally using ion-specific electrodes. However, mixed ligand complex formation with humic and fulvic acids has not received widespread attention, despite these results and their potential importance.

Finally, humic and fulvic acids can act as chemical weathering agents by complexing reactions. Early work was carried out on metal oxides[244] and the differential leaching of cations leading to the decomposition of rocks and minerals is frequently cited.[1] Many early experiments on the role of humic and fulvic acids in the breakdown of rocks and minerals are summarized by Ong *et al.*[245] There is no doubt that chelation of metal ions by humic materials is of great importance in this respect. Furthermore, the process might be responsible for the formation of lateritic aluminum deposits, which are restricted to tropical climates which have an abundance of humic acids in soils and waters. Humic acids possibly are involved in the dispersion of metals from ore deposits, by reaction with both primary and secondary minerals. Experiments show that galena and blende are rapidly attacked by a podzolic soil humic acid extract;[246] the study was extended to ore metal oxides, secondary minerals and various components of gangues. Typical extraction results for the sulfides were 0.12 mg per day of Zn from blende and 3 mg per day of Pb from galena using a 0.1% (w/v) aqueous solution of the humic acid preparation. These values are much higher than for rain and other near-surface waters and it was suggested that the concept of relative metal mobilities near ore bodies might need to be reassessed in environments which contain large concentrations of humic and fulvic acids.

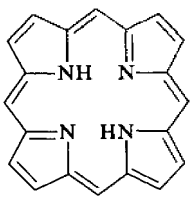
64.5.2 Complexes of Porphyrins and Related Macrocyclic Ligands

The origins of organic geochemistry could be traced to the pioneering studies of Treibs[247,248] who discovered that a number of petroleums and bitumens contained porphyrins. Later studies confirmed metal complexes of porphyrins in such organic media as well as in shales and the conclusion that the ligand was in fact deoxophylloerythroetioporphyrin (DPEP; **6**), a degradation product of the chlorophylls, was taken as proof that chlorophyll-bearing plants were primarily responsible for the formation of petroleums and other asphalts. This monumental discovery has prompted numerous researches in this field, signifying as it does the continuity of life forms similar to those present today on the earth from early times. Vanadyl porphyrins have been isolated from shales at least one billion years old.[249]

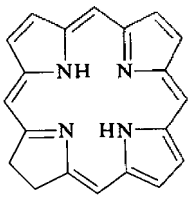
Metal complexes of porphyrins involving Mg^{II}, Ni^{II}, V^{IV}, Fe^{III}, Ga^{III} and Cu^{II} have been identified from a number of sediments. Early work in this area has been summarized by Saxby,[186] and a

recent review[250] of the many types of tetrapyrroles found in the geosphere has placed much of the published organic and coordination chemistry of these compounds in perspective. Nevertheless, it has only been over the last year or so that the definitive structural evidence proving the link between chlorophyll and many petroporphyrins has been forthcoming.

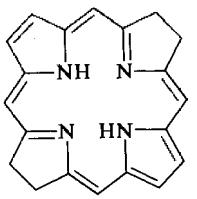
The metal complexes found in geological media are based on four classes of ligand: the porphyrins, the simplest being porphin (**19**), dihydroporphyrins (chlorins) (**20**), tetrahydroporphyrins (**21**) and the corrins (**22**). These in turn are generally thought to arise from the breakdown products of the chlorophylls, haem-type centres, especially the cytochromes, and related complexes such as vitamin B_{12} and nirrins, associated perhaps with metal enzymes in methanogenic and allied bacteria.



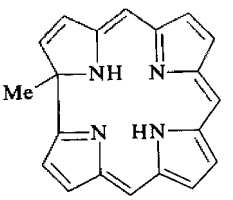
(19)



(20)



(21)

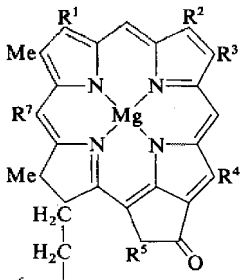


(22)

While the detailed molecular arrangement of most geoporphyrins is not known, much chemical evidence has accumulated concerning the basic structures of the ligands and complexes involved. Their general geochemistry and distribution in soils, sediments and rocks ranging in age from the Precambrian to the present has been elucidated.[251] In sedimentary rocks and asphalts, porphyrins are predominantly present as Ni^{II} or VO^{2+} complexes. This has been attributed to the great stability of these coordination complexes and it is thought that the formation of the coordination compounds themselves confers the overall resistance of the ligands towards degradation during the usual later diagenetic processes. However, early workers[252,253] also noted the presence of Fe^{III}- and Cu^{II}-containing species. As is only to be expected, the concentrations of metal porphyrins in geological media are highly variable. Ni^{II} species amount to some 10 p.p.m. in sediments and Fe^{III} complexes are present at roughly the same levels. Vanadyl compounds are comparatively more concentrated in marine horizons. In asphalts, complexes can be present at about the 0.1% level, but are most frequently represented at much lower concentrations.

These comparatively low concentrations are no doubt responsible in part for the lack of detailed molecular structures in the literature. Coupled with this is the fact that complex mixtures are invariably isolated in the first parts of most procedures; the number of isolated single species is rare indeed. Chromatographic results, volatility studies and powder X-ray data all pointed at an early date to the presence of groups of isomers in isolate fractions rather than the presence of unique compounds.[254] Finally, the application of mass spectroscopy to the study of petroporphyrins clearly established that this was the case, revolving about classic studies involving material isolated from a Swiss oil shale and units from the Green River, Colorado, oil shale.[255,256] One important fact emerged from these investigations. This was that porphyrins and their complexes (the compounds being demetallated prior to mass spectrographic analysis) occur in homologous series which arise from variations in the number and nature of alkyl substituents at peripheral sites of the basic macrocycles (**6**), (**19**)-(**21**). Observations of peaks in the series $310+14n$ and $308+14n$ ($n \geq 2$) attest to increasing degrees of alkylation in the ligands based on porphin and a DPEP, respectively. This compelling evidence was presented some time ago and is summarized in a short review of early work in this field.[257] Most frequently, masses of from 450–500 are found for fossil porphyrins in sediments and asphalts. Generally, DPEP itself is the largest component of most mixtures although etioporphyrins related to the haem family, but also possibly arising from chlorophylls by the opening of the exocyclic ring, can be present in comparable or greater amounts. Furthermore, significant amounts of either series containing as few as eight or as many as 20 or so methylene groups can be present, although concentrations usually drop off with either decreasing or increasing molecular weights.

Inhomogeneity is quite naturally predicted to occur in this class of complexes. This is not only due to the different possible breakdown pathways in soils, sediments, *etc.*, but is also due to the multiplicities of naturally occurring precursors in living organisms. For example, a number of known chlorophyll structures are shown in (**23**). The structural complexity is even more elaborate for the haems. Mixtures in geological media thus are to be expected. However, it should be pointed out that the amount of porphyrins from plant sources is overwhelming compared to that

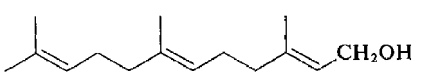


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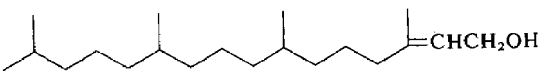
$R^1 = CH{=}CH_2$, CHO, CH(OH)Me
R^2 = CHO, Me
R^3 = Et, Pr, Bu^i
R^4 = Me, Et
R^5 = H, CO_2Me
R^6 = phytyl, farnesyl
R^7 = H, Me, Et

from animal sources (by the order of about 10^5 by weight) and it is probable that the majority of the haem geocomplexes also arise from plant pigments other than, and *via* particular degradations of, chlorophylls rather than from animal remains.

In the original work mentioned above, Treibs outlines the general mode of decomposition of the chlorophylls in sediments and so on. Magnesium is lost first: this reaction proceeds with ease and it is possible that other metals are coordinated at an early stage. In agreement with this notion is the fact that Ni^{II} and VO^{2+} stabilize the overall porphyrin structure, and that Ni^{II} chlorins have been isolated from recent freshwater muds.[258] These reactions are followed by ester hydrolyses, vinyl group hydrogenation, oxidation of the chlorin to the porphyrin, reduction of the carboxyl group(s) and decarboxylation. It is of interest to note that isoprenoids in sediments and asphalts are almost certainly derived from farnesol (**24**) or phytol (**25**). The same can be said of numerous other fatty acids and related molecules also present in such and related media.[259] Such a scheme of degradation leads naturally from chlorophyll *b* or bacteriochlorophyll to DPEP, the product advanced by Treibs. Variations of stereochemistry and isomeric distributions since observed have been ascribed to transalkylation reactions or radical combinations with alkenes of different molecular weight. It should also be remembered that ligands based on (**20**) and their metal complexes may also be generated from those based on (**6**) *via* the opening of the exocyclic ring if the ester hydrolyses occur under basic conditions.

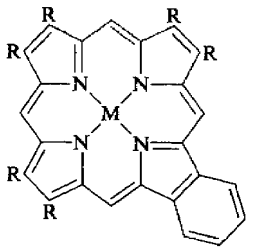


(24)



(25)

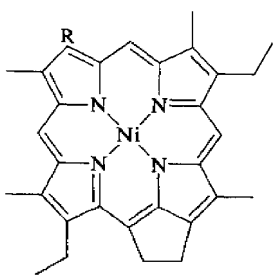
Aside from mass spectroscopy, the most frequently applied technique to the study of petroporphyrin and other geoporphyrin complexes is electronic spectrophotometry, and this formed the basis of the original identifications. Distinctive visible and electronic spectra, especially concerning the so-called Soret bands,[260] have been extensively utilized for gross structural determinations. Details can be found in the general reference given above. Four main bands are evident in the visible region of the electronic spectra of the free ligands, which correspond generally to the four main structural types. These are DPEP, and the etio (alkyl substituted), phyllo ($-CH_2CH_2CO_2H$) and rhodo ($-CH_2CH_2CO_2H$ and $-CO_2H$) series based on the nucleus of (**19**). The visible region of the electronic spectrum is fairly sensitive to structural alterations of the ligand, and the organic molecules are usually red in colour. This fact distinguishes, in most cases, ligands based on (**19**) from those based on (**20**), which are green. A somewhat different picture emerges concerning the visible electronic spectra of metalloporphyrin complexes, which are dominated by two bands. In non-coordinating solvents, Ni^{II} etioporphyrins show a distinctive spectrum characteristic of a square planar complex with maxima around 550 and 510 nm. The corresponding square pyramidal VO^{2+} complexes have maxima around 570 and 530 nm. Extensive discussion of spectral interpretations has appeared.[250,251,257] Indeed, the postulated existence of some porphyrins observed in mass spectral studies relies on such work. One example is a series based on (**26**) which has been noted from a number of geological sources.[261] Other related complexes, reminiscent of the phthalocyanines, which contain more than one condensed benzene ring, may also be present in sediments and asphalts. No chlorophylls with related structures are known, however, and the origin of such complexes remains rather enigmatic. It is possible that they derive from reactions of other complexes with aromatic fragments in asphalts. Several workers have presented evidence of high molecular weight porphyrin-containing complexes in oil shales and other materials.[262,263] The porphyrin complex nuclei may be bonded to kerogen during diagenesis. Peptides and proteins may also be linked to the central coordination complex in some cases.[263,264] Gel-permeation studies have indicated some very high molecular weights.



(26)

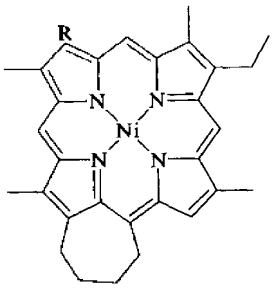
Treibs isolated the first porphyrin coordination complex from a Swiss marl,[265] and showed that it (or at least a structurally related derivative) occurred in a wide variety of sedimentary rocks and asphalts. He showed it to contain vanadium and subsequently the involvement of the vanadyl ion was proved.[266] Treibs also described a second chelate from the same original source, which he proposed to be an iron complex. Somewhat later it was shown that the complex contained the Ni^{II} ion. It is thus appropriate, and in view of much of the foregoing discussion, to focus attention on the detailed structure of the few fully characterized geoporphyrin complexes recently reported, since their elucidation crowns some five decades of intense activity in this area of coordination geochemistry.

High resolution ^1H NMR techniques have proved to be of immense help in this area.[268,269] Very recently, Fookes reported[270] the separation of Ni^{II} porphyrins from the Julia Creek oil shale from Queensland, Australia. The original material contained some 11 p.p.m. of Ni complexes in all and these were separated by a combination of TLC and reverse-phase HPLC procedures. The mass spectra of two of the fractions displayed patterns indicating that they were composed of single complexes, one corresponding to Ni^{II}—DPEP and the other to one of its C_{30}-homologues. In a series of elegant experiments involving the exhaustive use of the nuclear Overhauser effect (NOE) it was unequivocally established that the first complex was indeed that shown in (**6**) and that its congener was that shown in (**27a**). Previous workers[271] had reported a partial structure determination. These outstanding results finally proved the long-assumed link between chlorophylls and petroporphyrins and their complexes. A third Ni^{II} complex was isolated and it corresponded to a C_{31}-homologue as evidenced by its mass spectrum. A full characterization of this species by NOE spectroscopy established this species as that shown in (**27b**). In addition, X-ray crystallographic evidence has been forthcoming. The major vanadium-containing complex from the Julia Creek oil shale was crystallized and a structure determination has shown it to be the VO^{2+} analogue of (**6**).[272] The final structural proof concerning these complexes so long sought by so many workers has thus now been provided.

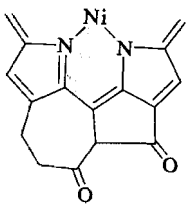


(**27a**) R = H
(**27b**) R = Me

Fookes has also reported[273] the structural characterization of a homologous series of 15,17-butanoporphyrins from the Julia Creek material. The three homologues are shown in (**28a–c**). Other workers[274] have also established the presence of the free ligand of (**28b**) in the Serpiano oil shale. In this study, the ligand was derived from the vanadyl complex. The variation in both series of complexes characterized with respect to substitution at C-3 could be accounted for by the original presence of a vinyl group at that position but the origin of the seven-membered ring in (**28**) is obscure in that it is not known in any present-day chlorophyll, although it may have arisen from an extinct species. Alternatively it could be derived *via* the condensation of the propionic side chain with the exocyclic ring as shown in (**29**).[273] Subsequent hydrolyses, reduction and decarbonylations could lead to the observed species. It is anticipated that further related characterizations of individual species will yield valuable clues as to the origin of such complexes and their bearing upon evolution trends concerning extinct species.

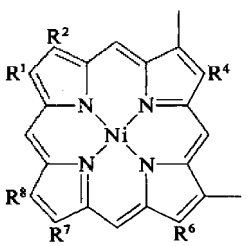


(**28a**) R = Me
(**28b**) R = Et
(**28c**) R = H

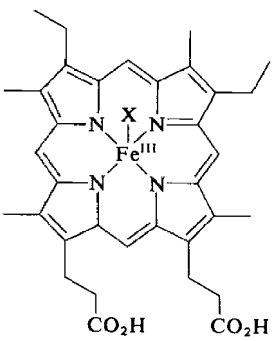


(**29**)

A few unambiguous characterizations of metal porphyrins not containing an exocyclic ring have also been recently reported. Gilsonite is a generic name given to a complex bitumen from the Unita Basin, Utah, USA. It is known to contain a reasonably simple distribution of etio- and DPEP-based nickel porphyrins on the basis of a series of mass spectrographic and chromotographic studies.[261,275] Up to about 100 p.p.m. of Ni^{II} species are present in the gilsonite. Two etioporphyrins (**30a,b**) have been demonstrated to be present. Their characterization was achieved, however, after removal of Ni^{II} from the complexes.[275,276] The identity of the complex involving etioporphyrin III (**30b**) was proved using a novel NMR technique involving the preparation of a double sandwich complex of the type bis(porphyrinato)mercury(II)acetatomercury(II).[277] This kind of adduct might prove to be of importance in the future in the identification of other porphyrin complexes of geological origin. A particularly noteworthy feature of this Ni^{II} etioporphyrin species is the fact that it is clearly derived from chlorophyll *a*, the most abundant of the naturally occurring chlorophylls. The exact point in the degradation of chlorophyll *a* at which the exocyclic ring is opened is not known, but it has been shown[278] that etioporphyrins are transformed from members of the DPEP series if they are heated in clay mixtures. This process is quite analogous to those occurring during diagenesis of the sedimentary column.



(**30a**) R^1 = Et; R^2-R^8 = Me
(**30b**) R^1, R^8 = Me; R^2, R^4, R^6, R^7 = Et
(**30c**) R^1, R^7 = Me; R^2, R^4, R^6, R^8 = Et



(**31**)

Recent evidence has come to light that geoporphyrins and their complexes may indeed have a mixed origin. This conclusion was drawn on the basis of the isolation of mesohaem (**31**) from an Australian lignite.[239] The concentration of the porphyrins present was less than 1 p.p.m. The natural material was demetallated, converted into its dimethyl ester, and the ^1H NMR spectrum of its Zn^{II} complex was found to be identical to that of an authentic sample. The Fe^{III} atom present in the original complex might have been that originally incorporated into the macrocycle during biosynthesis. The elucidation of the mesohaem geoporphyrin structure indicates therefore that it and other related complexes might arise in sediments and other media *via* the degradation of various cytochromes. The same group has also reported the isolation of a number of gallium(III) porphyrins from a bituminous coal.[280] One of the components of the mixture of gallium complexes had the required molecular weight for, and the same retention time in HPLC experiments as, the synthetic hydroxogallium(III) etioporphyrin I chelate (**30c**). Of the corrin (**22**) series of complexes comparatively little is known. Vitamin B_{12}, the Co^{III} complex based on this ligand, and its congeners are known to be present in seawater.[187] It is however quickly metabolized and migration of Co^{III} in muds and related sediments is primarily controlled by biological activity involving the more or less intact vitamin or its derivatives.[281]

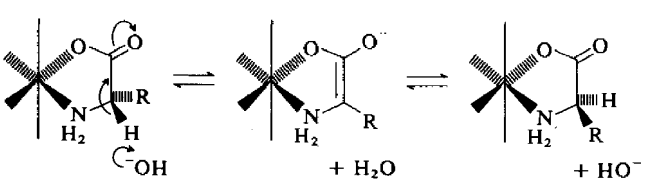
The complete structures of but few geoporphyrins have been established. This state of affairs does not bring into question the enormous volume of work on such naturally occurring coordination complexes which can be gleaned from the general references given. Quite the contrary! The most recent work provides the final confirmation of the scheme of Treibs and thoroughly establishes the link between living organisms and tetrapyrroles and their complexes observed to be widely if not abundantly distributed in rocks and asphalts. It is anticipated that in the near future many more such detailed studies will be reported as a result of advances in instrumentation, especially those in the field of high resolution NMR spectroscopy. Results of this nature are essential for a complete understanding of the origin of the complex mixtures of porphyrin complexes found in nature and indeed to shed light on evolutionary processes which have taken place over the last few billion years.

64.5.3 Complexes with Other Organic Ligands

Organic geochemists have now isolated many hundreds of organic compounds[187,206] from natural waters, soils, sediments and rocks dating from the present time back to the Precambrian era.[282] Indeed, a considerable number of these species are potential ligands containing the usual donor groups based on elements in groups V and VI of the periodic table, and perhaps others. However it is only fair to conclude that the coordination geochemistry of these ligands has not been deeply studied in the sense of the isolation of individual complexes. The main reason for this is probably concerned with experimental procedures adopted for the separation of the ligands themselves; extraction of sediments and so on with strong mineral acids is not particularly conducive to preservation of many of the potential complex molecules. Nevertheless, the presence of the ligands in environments rich in metal ions available for complexing, taken together with our knowledge of the formational stabilities of certain chelates reported elsewhere in this compilation of reviews, makes it inconceivable that numerous kinds of coordination complexes of ligands other than humic acids and porphyrins do not exist in a wide variety of geological environments. A number of the probable interactions, some of which are potentially of great importance, are mentioned below.

Amino acids are widespread in nature and have been isolated from all waters and rocks, except igneous and highly metamorphosed units, together with peptides and proteins.[283,284] Complex formation is overwhelmingly probable in these circumstances and a few examples put forward in the literature are worth enumerating.

The rates of racemization and epimerization of amino acids in sediments and fossil remains have received increasing attention with respect to application as a possible dating method.[285,286] The most extensively studied materials are the calcareous tests of pelagic formanifera, which are abundant in marine sediments. These are biomineralized substances consisting of polypeptides and proteins embedded in calcium carbonate and related mineral matrices.[287] Amino acids are released slowly by hydrolysis and undergo a series of degradations as well as being racemized. Racemization rates vary from amino acid to amino acid as might be expected; equilibrium has been observed in Miocene samples.[288] Recently it has been shown that metal ion catalysis of the racemization of amino acids may be important in geological environments and such reactions may give rise to misleading dates. The generally accepted scheme for the reaction is shown in Scheme 2. Of course, diastereoisomeric amino acids may give rise to equilibrium constants not

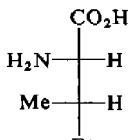


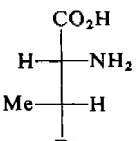
(32) (33) (34)

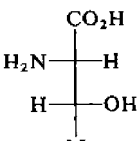
Scheme 2

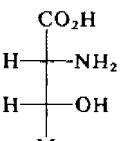
equal to unity. Early evidence for this kind of metal ion catalysis involving a coordination complex was presented by Bada and Schroeder.[289] They observed that the rate of epimerization of (*S*)-isoleucine (**35**) is about an order of magnitude greater than would be expected on the basis of experimentally determined reaction rates. In addition, it was noted that (*R*)-alloisoleucine/(*S*)-isoleucine ratios, (*R*)-alloisoleucine (**36**) being the product of epimerization in this case, were

higher in the free amino acid pool compared with the protein fractions. It was suggested that divalent alkaline earth complexes were probably responsible for the catalysis, and that these derived from the calcareous mineral of the samples. Other metal ions, notably Cu^{II}, were also suggested as being important. More recently, analogous catalysis *via* coordination complexes has been proposed for the (*S*)-threonine (**37**)-(*R*)-allothreonine (**38**) epimerization in fossil foraminifera.[290] Other dating discrepancies found for fossil corals[291] may also derive from related reactions. Many metal ions, particularly of the transition series, could be involved, and are known to participate in these epimerizations. However, their mode of action is complex[292,293] and much more work is required to evaluate their significance in a geological context.

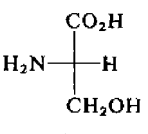

(**35**)


(**36**)


(**37**)

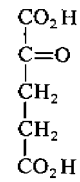

(**38**)

Threonine and allothreonine are thermally unstable amino acids. The same is true for the simplest hydroxy amino acid, (*S*)-serine (**39**). High levels of this amino acid have however been reported from certain petroleum brine waters[294] and its preservation may be due to the formation of stable chelates. Ahrens[295] has suggested that metal–amino acid chelates may be important in the sedimentary cycle, and the uptake of certain metals in sediments, particularly in binding of metal–amino acid chelates to clays, has been proposed as a possible mechanism for the incorporation of metal ions in carbonaceous materials.[296] Similar complexes are thought to contribute to the stabilization of amino acids in coals, lignites and peats,[297] but, as has been outlined in a previous section, many other ligands are also present in these media, and their relative importance is difficult to assess. Much of this work is unfortunately of a speculative nature since no well-characterized complex of an amino acid has been isolated from a geological source, as far as the author is aware.


(**39**)

Many other nitrogen-containing species which are perfectly capable of forming complexes with metal ions have been isolated from sediments, rocks and asphalts. Among them are pyridines, pyrimidines, quinolines, indoles, purines and the like, as well as pyrroles, imidazoles, nucleic acids and amino sugars.[294,298–300] In addition many sulfur compounds have been reported, especially from petroleum,[301] and these contain potential ligating sulfur atoms as thiols and thioalkane fragments in bulky thioalkanes and heterocyclic molecules. However, while the potential exists for complex formation with these ligands, little is known at the molecular level of their participation in geochemical coordination cycles.

Somewhat more detailed information is available concerning complexes of carboxylic acids. Hyden[184] was among the first to suggest that trace metals in crude oil were at least partially present as salts or complexes of organic acids. Similarly, Soviet workers have suggested that these kinds of complexes are important in sediments and rocks.[302] Carboxylic acids are the major oxygen-containing components of crude oils[303,304] and short chain aliphatic acids including acetic, propionic, butyric, isobutyric, valeric and isovaleric acids have been isolated from oil field brines.[305] Phenol and phthalic acids were also detected in these media. The occurrence of hydroxy acids in sediments has been recently reviewed[306] and low molecular weight acids including the above, together with oxalic, malic, 2-ketoglutaric, tartaric, lactic and citric acids have been isolated from soils and sediments.[197,307] Interactions with metal ions of the aromatic members mentioned above (and their congeners) have been covered in a previous section. Attention is also drawn to the fact that some of these ligands occur as coordination complexes in isolated mineral species as listed in Section 64.2.2. Thus there is no doubt that the coordination geochemistry of these substances is ubiquitous even though few complexes have been isolated intact. Tightly bound α-hydroxy acids observed in recent sediments might owe their resistance to extraction to participation in complexing on mineral surfaces.[308]



(40)

Mineral weathering, or at least that part due to the exudation of chelating agents by microorganisms, is probably the best-studied area of coordination geochemistry involving organic oxygen-containing ligands. This subject has been recently reviewed in an authoritative manner[309] and many examples have been reported. Simple chelating acids including those mentioned above as well as salicylic and 2,3-dihydroxybenzoic acids are formed by microorganisms. The simple species 2-ketoglutaric acid (**40**) has been shown to be important during the microbial weathering of silicates and forms complexes with Ca^{II} during the solubilization of calcareous rocks, apatite and montmorillonite. Citric and oxalic acids also contribute to the destruction of silicate and other rocks by coupling with Fe^{III}, Al^{III} and Ca^{II}. Several workers have conducted experiments along these lines and results indicate that chelate formation with all of these kinds of ligands is responsible for a wide variety of mineral transformations.[310-313] Other workers have identified an Ni^{II}–stearic acid complex spectroscopically in a hectorite clay,[314] and other kinds of ligands derived from microorganisms might also be important in the geochemical cycle. A number of gallic acid complexes of aluminum have been studied by EMF titration techniques and stability constants have been computed.[315] The possible role of these complexes in the geochemistry of natural waters was assessed and it was shown that kaolinite solubility can be increased about five-fold at neutral pH. Hydroxamic acids may also be important in related systems.[309]

A comment on possible interactions of metal ions with sugars and polysaccharides in the neutral environment is warranted. Metal ion incorporation into algal mats was mentioned in Section 64.5.1, in which bonding to sugar residues as well as to amino acidate groups was probably involved. Many sugars have been reported from seawater and sediments[316] and metal incorporation into detrital polysaccharides and alginates has been suggested to be important in seawater.[317] Experiments describing the extraction of uranium from solution by chitin and its derivatives have been reported.[318] Related processes may control in part the distribution of uranium in natural waters. Again, however, it must be said that the true role of such ligands in the geochemical cycle is of a speculative nature. The challenge remains for geochemists and coordination chemists to evaluate fully the occurrence and importance of such complexes. Of paramount concern, it would seem, would be the isolation and characterization of some of the many chelates which undoubtedly exist in natural waters, soils and rocks.

Finally, attention is drawn to the possibility of organometallic complexes in the natural environment. We do not wish to examine alkyl metal species such as methylmercury and dimethylmercury compounds, important though these might be in terms of pollution studies. Their general occurrence is covered in a recent review.[189] Many alkenes are present in geological media but no evidence is available to suggest that π-complexes are formed. Mention has already been made of vitamin B_{12} and cyanide as a ligand in minerals, and more importantly in the potential mobilization of gold in its ores under near-surface weathering conditions. Conceivably, metal carbonyls could also contribute to metal ion transport at high temperatures under reducing conditions. A notable recent article, however, points out that organometallic complexes may be much more widespread in nature than is currently supposed. The report concerns the isolation of a number of organoarsenic compounds from the Green River oil shale and represents the first report of such complexes in fossil fuel precursors.[319] Both methyl- and phenyl-arsonic acids were shown to be present together with the arsenate ion. The phenyl-substituted compound is of some significance since no examples of biophenylation have been reported to date. Biomethylation of arsenic compounds, on the other hand, is well known. In this connection it should be noted that $AsMe_3$ is known to be produced by the action of certain microorganisms in soils.[197] One might anticipate that organogeochemicals might receive increasing attention in the future as a result of advances in instrumentation and activity in the field of pollution studies, especially those relating to the fate of metal-containing waste in the environment.

64.5.4 The Possible Involvement of Organic Coordination Compounds in Ore Formation

This is a field of potentially great significance, although it has received little attention to date, relying as it does on geochemical inference rather than a solid foundation of experimental fact.

A recent article[122] has highlighted the possibility of the transport of Pb^{II} as organic complexes in Mississippi-type ore solutions. Development of a purely inorganic model for metal complexing and transport gave rise to estimates of Pb^{II} concentrations which are probably too low to account for the volume of mineralization found in these deposits. Evaluation of stability constants for metal acetate and related species indicated that such complexes were unlikely to enhance the concentration of Pb^{II} in the ore-bearing fluids to the levels thought to be involved. However, if salicylic acid had been present, a considerable increase of Pb^{II} in solution as a complex would result. While salicylic acid has not yet been detected in oil field brines, from which the transporting solutions are thought to originate, either it or a structural analogue could have given rise to the observed metal orebody distribution.

Mention has already been made of the accumulation of uranium by organic material, predominantly in the form of humic acid-type complexes, and the involvement of such interactions in uranium ore formation. Other workers have suggested that the oxidation of organic compounds by hydrothermal solutions may give rise to a lowering of the solution redox potential.[320] This was suggested to play a part in the crystallization of uranium in certain deposits of the Bohemian massif. Isoprenoid hydrocarbons, amino acids and fatty acids are all associated with copper, uranium and hydrothermal fluorite deposits of the region, and may all have been involved in complex formation. Related studies by earlier Soviet workers[321] have commented on amino acids present in fluorites from the Azov region. In mineralized limestones, glycine, alanine and valine were detected and the distribution of Cu, Pb, Ga, Sb, Co, Mo and other metals was explained by complex formation between the ligands and metal ions.

Methane is a common component of fluid inclusions in minerals from many hydrothermal deposits. Low molecular weight hydrocarbons of various sorts are also present. Kranz[322] has summarized the early work in this field. Alkanes, alkenes and alkylbenzenes were all present in a number of inclusions in fluorite, together with fluorinated hydrocarbons, that he studied from several European localities. In addition the donors methylamine, dimethylamine and ethylamine, together with glycine, alanine and aminobutyric acid, could be isolated from the fluorites and feldspar inclusions. It was concluded that these substances probably derived from the degradation of humic acids and the like and could have been important in the transport of metals as complex ions. In a later study[323] a number of nitriles together with amines and amino acids were reported from uraniferous fluorites. A high correlation between U and Th contents in the samples and the organic material was taken to indicate that the organic material was intimately linked with metal transport. It was also suggested that the amino acids themselves might not be of biological origin but could have been synthesized as radiochemical products of reactions of hydrocarbons, ammonia and water in the ore-forming fluids.

On the other hand, some model studies indicate that in certain sulfur-rich marine waters the concentrations of amino acids and simple organic acids are too low to much effect metal speciation in solution. The possible importance of humic complexes was again emphasized in these environments. In this connection, such complexes have been proposed to be important in the generation of certain stratiform base-metal orebodies.[325] Sulfur could be contributed to the system from components of the humic acids themselves. Metal sulfides were precipitated in an experimental investigation from deoxygenated suspensions of metal humates. Framboidal textures, frequently observed in sulfide assemblages from such deposits, may also result from the decomposition of metal humate complexes. In a related study of the Carlin gold deposit,[326] humic substances associated with the mineralization were suggested to have been responsible for the gold deposition. Gold complexes such as $AuCl_4$ or $Au(CN)_2^-$ are thought to be taken up as complexes involving chelation by N, S or O donors prior to reduction to metallic gold. The concentration of copper in the Kupferschiefer of Northern Europe has also been attributed to organic complex transport of the element.[327] While humates are most probably involved, experiments involving tannic, salicylic and citric acids indicated that these or related ligands could also be implicated in copper mobilization. Finally, the transport of manganese by organic acids has been proposed as a mechanism for the formation of a number of ores of this element.[328] The geochemical cycle of manganese is intimately associated with microbial activity,[329] and some of the ligands mentioned earlier might be involved in its complexation and mobilization. Humic acids and their breakdown products may also be important. Brockamp's experiments[328] with these species, salicylic, citric and tannic acids give rise to a reasonable explanation for the origin of various marine sedimentary manganese deposits.

There seems little doubt that coordination geochemistry does play a role in ore formation in a number of environments. Much more work in this field remains to be done however. It is possible that sedimentary iron formations also derive from similar cycles to those mentioned above for manganese.[330] The uptake of iron by bacteria which are capable of synthesizing magnetite, Fe_3O_4,

in vivo could lead to the deposition of sediments containing significant proportions of that mineral. A proper assessment of complex formation on ore depositions, while offering a tempting and plausible explanation for some geological settings, must however await more rigorous experimental investigation.

64.6 PREBIOTIC SYSTEMS

It is widely accepted that the Earth condensed from a gas cloud about 4.5 billion years ago. The age of life on Earth is not precisely known but the earliest microfossils and stromatolites found in the Warrawoona formation are 3.5 billion years old. Naturally, living organisms must be older than this but the time for their development must be of the order of around 0.5 billion years if the probability that the Earth was molten early in its history is taken into account.[331] While some authors have argued for panspermia as the origin of life on earth, this view is not widely held and it is generally acknowledged that life arose *via* a series of reactions in aqueous solutions containing various organic compounds, the 'prebiotic soup'.

This possibility was first advanced by the Russian biochemist Oparin, who outlined the notion of spontaneous generation of life on the primitive earth. Independently, Haldane[333] reached much the same conclusions and demonstrated that it was possible that significant concentrations of organic chemicals could have been built up in the early oceans. These ideas have been expanded upon by other workers.[334,335] Of course, the prevailing chemistry of the atmosphere and the oceans of the primitive earth is a highly contentious subject. The general inorganic coordination chemistry outlined in previous sections of this review is still applicable, albeit that certain simple ligands such as cyanide or sulfide may have been present at higher concentrations, and other species, particularly more oxidized ones, were probably present at much lower levels. In the light of the coordination chemistry covered above, little more needs to be added on these subjects here. Rather, the role of coordination processes and complexes in the chemistry of formation of prebiotic organic compounds will be examined. Again it must be emphasized, however, that the significance of such reactions is speculative in the extreme, though it seems inescapable that coordination complexes must have played a prominent part. The reasons for thinking this are the experimental results amassed on the synthesis of organic compounds in the presence of metal ions under simulated prebiotic conditions, the synthesis of many classical ligands in related experiments, and the fact that it appears that living organisms incorporated coordination compounds in their metabolic cycles at an early date. This latter chemistry has persisted throughout evolution and coordination complexes are indispensable for all living organisms.

The atmosphere of the primitive earth was probably highly reducing with carbon, nitrogen, hydrogen and oxygen being overwhelmingly present as methane, nitrogen, hydrogen and water, although not all authors have agreed with this view,[336,337] because little carbon is found in the oldest known sedimentary rocks. On the other hand, it must be remembered that changes in the atmosphere to its being one in which carbon was present as CO_2 could have occurred by the time that these rocks were laid down. Other compounds containing the above elements in the primitive earth were perhaps mineral carbides, water of crystallization in various mineral species and ammonium ion or ammonia. Much of the argument concerning the composition of the primitive atmosphere has been put in perspective in two excellent reviews.[331,338] The second draws upon our knowledge of other planetary atmospheres, the composition of meteorites and the known early deposition of large amounts of iron in Precambrian sediments. This, and particularly the first, points to the general conclusions recorded above, coupled with the fact that prebiotic generation of organics places reasonably tight restrictions on the atmospheric composition in any case. The prime energy sources for the reactions of interest are generally agreed.[331,338] Of overwhelming importance is radiation from the sun. Of less significance is energy from electric discharges. Radioactivity, volcanic activity and shock waves together with cosmic rays and the solar wind probably made negligible contributions to the reactions in the prebiotic soup. Thus it is understandable that most experiments on synthesis in prebiotic systems have used UV or sparking sources in various mixtures.

With these kinds of experiments in mind, Beck[339] has elegantly deduced some of the important simple coordination chemistry of the prebiotic soup. He suggests a primary ligand set of H_2O, NH_3, CO, CN^-, $(CN)_2C_2^{2-}$, S^{2-}, H^-, N_2 and CO_2. Some of these species are of importance in reactions to form complex organic molecules, as discussed below. Cyanide complexes were possibly important in the primitive oceans, and experiments on extraction of elements from powdered rock samples have shown that significant concentrations of Fe, Co, Cu, Mn and Mo

can be generated by complexing and dissolution.[340] Earlier workers have also commented on cyanide complex formation,[341,342] and such species may be involved as catalysts in other reactions of prebiotic interest. Beck[339] also pointed out that 'it is inevitable to realise that exotic transition metal complexes, which can be prepared using special laboratory techniques, could have been a common species on the primordial Earth.' This statement is undoubtedly true and unopen to challenge. However, the nature of such complexes is impossible to discern fully in the sense that as many complexes might be suggested as the imagination permits. The general chemistry of the simple ligand set mentioned above is known, and has been expounded upon at length elsewhere in this compendium of reviews. Typical, simple inorganic complexes, present in the primitive oceans, are easy to imagine, and their chemistry is accepted in this connection to be well established. One particular set of species, that involving sulfide ligands S_n^{2-}, is perhaps worth mentioning in some greater detail. Given a reducing environment, these kinds of complexes may have been widespread. The connection between them, minerals such as pyrite, FeS_2, and its congeners, and the iron-sulfur cluster enzymes,[343] now known to be basic to all present life-forms, is easily brought to mind. The evolution of iron-binding biomolecules has been reviewed.[344]

The first experimental evidence concerning the possible prebiotic synthesis of biological molecules was presented by Miller in 1953.[345] This study was in turn based upon that of previous workers[346] who found that CO_2 reacts to give aldehydes, among other products, in the presence of ionizing radiation. It was found that in a reducing atmosphere comprising CH_4, NH_3, H_2O and H_2, glycine, α- and β-alanine, aspartic acid and α-aminobutyric acid were produced by the passage of electrical discharges through the reaction mixture. Aldehydes and HCN were also produced, as were hydroxy acids, short chain aliphatic acids and urea. This remarkable experiment has prompted an enormous amount of experimentation in the field, almost all of it patterned after the original work. It is intriguing that glycine in particular should be formed in such high yields as were found (about 2%, based on carbon) and that amino acids are formed as easily and abundantly in such simple systems. We must draw the inescapable conclusion that amino acids form the basis of life as we know it by virtue of their ease of formation under primitive Earth conditions. Miller has recently reviewed the work in this field stretching over three decades.[331]

Four mechanisms have been advanced for the prebiotic formation of amino acids. The first involves a cyanohydrin (reaction 2) and a related route (reaction 3) can be invoked to account for the presence of hydroxy acids. These particular reactions have been studied in considerable detail both kinetically and in terms of thermodynamic quantities.[347] An alternative route (4) involves the hydrolysis of α-aminonitriles, which are themselves formed directly in anhydrous CH_4/NH_3 mixtures.[348] Cyanoacetylene, formed in CH_4/N_2 irradiations,[349] yields significant amounts of asparagine and aspartic acids (reaction 5). Finally, a number of workers[336,350–354] have proposed that HCN oligomers, especially the trimer aminoacetonitrile and the tetramer diaminomaleonitrile, could have been important precursors for amino acid synthesis. Reaction mixtures involving such species have yielded up to 12 amino acids. Table 11 indicates the range of amino acids produced in these kinds of sparking syntheses. Of some interest is the fact that close parallels between these kinds of experiments and amino acid contents of carbonaceous chondrite meteorites exist.[331,355,356]

$$RCHO + HCN + NH_3 \rightleftharpoons RCH(NH_2)CN \xrightarrow{H_2O} RCH(NH_2)CONH_2 \xrightarrow{H_2O} RCH(NH_2)CO_2H \quad (2)$$

$$RCHO + HCN \rightleftharpoons RCH(OH)CN \xrightarrow{H_2O} RCH(OH)CONH_2 \xrightarrow{H_2O} RCH(OH)CO_2H \quad (3)$$

$$CH_4 + NH_3 \rightarrow H_2NCH_2CN + MeCH(NH_2)CN \xrightarrow{H_2O} H_2NCH_2CO_2H + MeCH(NH_2)CO_2H \quad (4)$$

$$NCC{\equiv}CH + NH_3 \rightarrow NCCH{=}CHNH_2 \xrightarrow{CN} NCCH_2CH(NH_2)CN \xrightarrow{H_2O}$$

$$H_2NOCCH_2CH(NH_2)CO_2H \xrightarrow{H_2O} HO_2CCH_2CH(NH_2)CO_2H$$

asparagine — aspartic acid

(5)

The role played by coordination complexes as templates and catalysts in these reactions is somewhat more difficult to discern, although several important results have been reported. Some early work by Bahadur[357] showed that amino acids were formed in the reaction of potassium nitrate with paraformaldehyde in the presence of light. Many amino acids were produced, but the highest yields were found when the reaction was carried out in the presence of iron(III) chloride as a catalyst. Later work[358] extended analogous findings to colloidal molybdenum oxide as the catalyst. Molecular nitrogen was fixed in this case, a reaction in a sense comparable to the

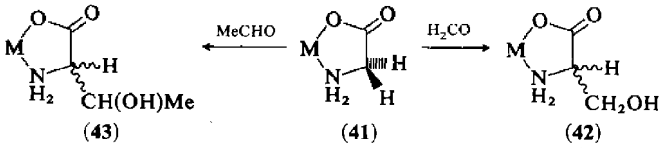
Table 11 Amino Acids Formed in Sparking Experiments with Mixtures of CH_4, N_2, H_2O and NH_3[331]

Glycine	α,γ-Diaminobutyric acid
Alanine	α-Hydroxy-γ-aminobutyric acid
α-Amino-*n*-butyric acid	α,β-Diaminopropionic acid
α-Aminoisobutyric acid	Isoserine
Valine	Sarcosine
Norvaline	*N*-Ethylglycine
Isovaline	*N*-Propylglycine
Leucine	*N*-Isopropylglycine
Isoleucine	*N*-Methylalanine
Alloisoleucine	*N*-Ethylalanine
Norleucine	β-Alanine
t-Leucine	β-Amino-*n*-butyric acid
Proline	β-Aminoisobutyric acid
Aspartic acid	γ-Aminobutyric acid
Glutamic acid	*N*-Methyl-β-alanine
Serine	*N*-Ethyl-β-alanine
Threonine	Pipecolic acid
Allothreonine	

well-known role of molybdenum-containing enzymes in the reduction of molecular nitrogen to ammonia in leguminous plants. Other workers[359] found similar results in the reaction of formaldehyde and hydroxylamine with added molybdate and vanadate. The yield of amino acids increased exponentially with added molybdate. Egami has most elegantly outlined the reasoning behind the accepted role of transition metal complexes in prebiotic syntheses involving Fischer–Tropsch-type reactions.[360,361] The trace metal composition of primitive seawater, especially concerning elements such as iron, copper, molybdenum and zinc, would be expected to influence syntheses and result in the incorporation of such elements into protoenzymes. Although some experiments involving Ni, Al_2O_3 and clay catalysts with CO, H_2 and NH_3 gave inconclusive results[362] about the role of the metals, later work[363] has shown that the original suggestions were most probably correct. Formaldehyde and hydroxylamine were reacted in a synthetic seawater in the presence of Zn^{2+}, MoO_4^{2-}, Fe^{3+}, Co^{2+}, Cu^{2+} and Mn^{2+}. Some 40 amino acids were detected in the products with glycine, alanine, β-alanine and norvaline being among the most concentrated. Of particular interest was the fact that peptides were also produced which also had some hydrolytic activity. The authors stated in view of this truly remarkable finding that 'this protoenzyme-like activity is in good correlation with the consideration by Egami that the zinc complex in the early stage of evolution may be regarded as a precursor of hydrolytic and transferring enzymes, including enzymes participating in the metabolism of macromolecules and information transfer'.

Reactions of coordinated amino acids and their precursors undoubtedly took place in the prebiotic soup. While it is impossible to assess the importance of such processes, we should allow ourselves a little speculation here, and a few examples are included, all of which are based on sound laboratory findings. Beck[339] observed the formation of glycine by the acid hydrolysis of the complex $H_2Cu_2(CN)_4(C_2N_2)$. It is possible that similar species might be involved in the prebiotic production of other amino acids. Serine and threonine together with allothreonine can be easily produced[364,365] by the reactions of coordinated glycine with formaldehyde or acetaldehyde (Scheme 3). Similar reactions to form ornithine and arginine are known.[366,367] Finally, reactions on clay surfaces, involving coordination complexes of amino acids and other ligands, may have elaborated the speciation of the prebiotic soup. Early work in this field has been gathered together by Weiss in an excellent review.[368] Under suitable conditions amino acids can polymerize in clays (and on SiO_2), among other important reactions. A recent report[369] has described the alteration of various aromatic amino acids, especially tyrosine, on kaolinite, bentonite and montmorillonite. Oxidative degradation occurs at pH greater than 3 and the possible role of clays in the prebiotic synthesis of polypeptides was assessed. The workers also found that (*S*)-tyrosine reacted faster than (*R*)-tyrosine, a result which contradicts the laws of thermodynamics, and which may have arisen as a result of bacterial contamination. A related result[370] concerning the supposed difference in stoichiometry of Fe^{III} and Fe^{II} complexes of, separately, (*R*)- and (*S*)-alanine, with a view towards the generation of optical activity in prebiotic systems is absolutely in error. This particular field of the origin of optical activity is the subject of much controversy[371,372] and a convincing explanation for the origin of handedness in biological systems is still awaited.

Perhaps one of the most important roles of clays and coordination complexes in the synthesis of prebiotic compounds, apart from their catalytic influences, is one of protection. Mention has



(43) (41) (42)

Scheme 3

been made earlier of the preservation of porphyrins by complexation, and it is possible that amino acids, among other species, were protected from other degradative reactions by the formation of complexes, and incorporation into clay minerals at the bottom of the primitive oceans. Much work remains to be carried out on these amino acid/complex systems, however, before any more definite conclusions can be reached.

Considerable attention has been focussed upon possible amino acid prebiotic syntheses in this section, because of their biological importance. It should be pointed out that many other compounds of biological significance have also been made under simulated primitive conditions and it is proposed to conclude this review with a brief examination of such reactions, particularly with respect to the possible role of coordination compounds in them.

Porphyrin complexes can be commonly produced in sparking mixtures. Thus, Hodgson and Baker[373] showed that pyrrole and paraformaldehyde in the presence of copper(II), nickel(II) and vanadyl salts give rise to both free and metal complexes of porphyrins. The most effective ion for the template reaction is Ni^{II}, a result parallelling the observations outlined earlier on the preservation of porphyrin complexes in asphalts, sediments and rocks. It was pointed out that coloured species noticed in earlier experiments[374] were also probably porphyrin coordination complexes. More recently it has been demonstrated[339] that $Ni(CN)_4^{2-}$ increases the yield of porphyrins in such reactions, as does $Fe(CN)_6^{2-}$. Since these ions were probably present in reasonable concentrations in the primitive oceans, their significance is obvious.

Nucleobase formation in a Fischer–Tropsch synthesis was first reported by Hayatsu[375] using a mixture of CO, NH_3 and H_2. This discovery was foreshadowed and expanded upon by a number of other workers and involves reactions of HCN or cyano complexes.[376–380] The later work by Hayatsu and coworkers[381] using Ni–Fe and Al_2O_3 catalysts is noteworthy. Alkyl cyanides, pyrroles, porphyrins, guanidines, hydantoin, uracil and derivatives, thymine, adenine, guanine, xanthine, melamine, alkanes, alkenes and aromatic hydrocarbons were all produced from the simple mixture originally used. It has also been shown that magnesium complexes in reactions involving urea and imidazole activate nucleotides and amino acids to form polymers.[382] Intriguingly, it has recenty been found[383] that Zn^{2+} and Pb^{2+} catalyze the polymerization of nucleotides with the production of oligomers some 30–40 units in length. The significance of these findings with respect to the prebiotic evolution of RNA polymerase was discussed. It is notable that all DNA and RNA are Zn^{2+}-containing enzymes. This research provides a vital clue to the early development of replicating systems.

Finally, the synthesis of sugars under prebiotic conditions has been achieved. This was really foreshadowed by the classic work of Butlerov[384] who demonstrated that pentoses and hexoses are formed by condensation of formaldehyde in basic aqueous solution. The process depends upon the presence of a suitable catalyst, usually Ca^{2+} derived from $Ca(OH)_2$ or $CaCO_3$, and alkaline earth complexes are most probably involved. Later workers, turning their attention towards prebiotic chemistry in particular, have shown that clays and apatite catalyze the formation of monosaccharides, especially ribose, with good yields being obtained.[385,386] Thus all of the main molecules of life, or their simple precursors and analogues, have been synthesized under conditions thought to approximate the primitive Earth. The role coordination complexes plays in these processes must be highly significant as evidenced by a number of experimental findings. Much more work remains to be done in this field, and on the involvement of mineral–organic interactions in the prebiotic soup. The role of minerals in these evolutionary pathways might be much more important than has previously been thought.[387]

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65

Applications in the Nuclear Fuel Cycle and Radiopharmacy

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65.1 INTRODUCTION

Coordination chemistry has played a crucial, though not always well defined, role in the isolation and utilization of metallic radionuclides. Some two billion years ago it was the differences in the coordination chemistries of U^{VI} and Th^{IV} which led to their geochemical segregation, and the subsequent formation of the richest uranium ore deposits available today. More recently, in 1898, the Curies exploited subtle differences in the chemistries of the metallic elements during their painstaking isolation of radium chloride by fractional crystallization of $BaCl_2$–$RaCl_2$ mixtures. In the same year, Marie Curie identified polonium and in 1899 Debierne discovered actinium. It was work such as this, carried out at the close of the 19th century, that laid the foundations for the modern radiochemical industry. Nowadays, tonne quantities of radioactive materials are routinely processed by the nuclear power industry and again coordination chemistry plays a central role in the separation processes used. As an adjunct to this exploitation of the actinide elements as sources of nuclear fission energy, the use of other radionuclides in a variety of applications has been developing apace. Nuclides such as ^{238}Pu and ^{90}Sr can provide reliable sealed heat sources which can operate continuously, without attention, for many years. These find applications in such diverse devices as heart pacemakers and spacecraft. Gamma ray emitting nuclides such as ^{60}Co may be used as radiation sources in, for example, the sterilization of

disposable medical equipment or the radiographic inspection of engineering components. The radiography of human patients is also possible using radiopharmaceutical agents containing short half-life γ-ray emitters such as ^{99m}Tc.

Three basic approaches may be used to generate 'man-made' radionuclides, two of which involve neutron irradiation of suitable target materials in a nuclear reactor. In one case this is to induce fission of a heavy nucleus such as ^{235}U in order to produce fission products such as ^{90}Sr, ^{99}Mo or ^{137}Cs. In the other case, neutron capture reactions are utilized in, for example, the conversion of ^{98}Mo to ^{99}Mo or the conversion of ^{235}U to ^{238}Pu. The third approach is only suitable in cases where small quantities of the product radionuclide are required since it involves the use of a particle accelerator to irradiate a target with ions derived from the nuclei of light elements. In all three approaches the isolation of the desired radionuclide will normally involve a separation process. Usually this process will include a wet chemical stage which exploits differences in the coordination chemistries of the metallic elements present.

In the case of radiopharmaceutical applications, not only is coordination chemistry involved in the isolation of metallic radionuclides but also in their incorporation into the active 'drug'. In fact the development of technetium radiopharmaceuticals represents a particularly timely and sophisticated application of coordination chemistry. In some ways this chemistry complements that of the nuclear fuel cycle. A large part of the basic chemistry involved in the reprocessing of nuclear fuels was developed in the post-war years between 1946 and 1970. Although many points of detail are still under investigation, the Purex process, which is most widely used today, employs the same basic chemistry as that developed in the late 1940s.[1] In contrast, major developments in the chemistry of technetium, especially as applied to radiopharmaceuticals, have occurred since 1970. This situation is to some extent reflected in the type of ligands used in these two different areas. Actinide separation generally involves hard 'inorganic' ligands such as water, nitrate, sulfate or organophosphate. Radiopharmaceutical chemists, on the other hand, are increasingly investigating the use of softer organic ligands containing groups such as amine, thiol or phosphine. Thus the historical development of coordination chemistry is, in some ways, reflected in the chemical systems used in the nuclear fuel cycle and, subsequently, in the formulation of radiopharmaceuticals. It is appropriate, therefore, to consider the nuclear fuel cycle, and the nuclide production processes which have developed in its wake, before turning to the use of radionuclides in pharmacy.

The coordination chemistries of the elements considered in this chapter have already been the subject of detailed discussion in earlier sections of these volumes. Consequently, it is the purpose of this chapter to review, in general terms, the nuclear fuel cycle, the production of metal radionuclides and subsequently their incorporation into radiopharmaceutical formulations. Within this framework, specific aspects of coordination chemistry which are relevant to the application in question will be considered.

Comprehensive accounts of the nuclear fuel cycle, including its chemical aspects, have been given, by Flagg[2] in a book published in 1967, and more recently by Wymer and Vondra.[3] More general texts on solvent extraction chemistry and separation methods for the rarer metals are also available,[4-7] along with compilations of papers relating specifically to actinide separations.[8] The uses of solvent extraction in the nuclear industry have been reviewed by Jenkins[9] and reviews of fuel reprocessing chemistry are given by Bond[10] and by Wilkinson.[11] Papers on solvent extraction processes may also be found in the proceedings of the International Solvent Extraction Conferences[12] (ISEC) held in Liege (1980), Toronto (1977), Lyon (1974), The Hague (1971), Jerusalem (1968),[12a] Gothenburg (1966),[12b] Harwell (1965),[12c] Brussels (1963)[12d] and Gatlinburg (1962).[12e] At least one section in these usually relates to the nuclear fuel cycle. The chemistry of nuclear fuels themselves has been described in reviews by Campbell[13] and by Marples *et al.*[14] Fast reactors have now been developed to the prototype stage and the results of work on the reprocessing of fast reactor fuels were described at an international symposium held at Dounreay in 1979.[15]

Turning to the subject of radiopharmaceuticals, a basic text on radiopharmacy is provided by Tubis and Wolf.[16] The chemistry of radiopharmaceuticals is described in a compilation of papers edited by Heindel *et al.*,[17] while the preparation of labelled compounds containing short-lived radionuclides has been reviewed by Silvestor.[18] Also Meares *et al.* have described the attachment of chelating groups to biological molecules to produce metal ion carriers which are selectively bound to sites within the test organism.[19] The metals most widely used in radiopharmaceutical applications are technetium, indium and gallium. In this context, recent reviews of technetium chemistry have been provided by Deutsch *et al.*,[20] by Davison and Jones[21] and by Schwockau.[22] The chemistry of gallium and indium which relates to radiopharmaceuticals has been reviewed by Moerlein and Welch.[23]

65.2 THE NUCLEAR FUEL CYCLE

The term 'nuclear fuel cycle' refers to the processes involved in the generation of power by the fission of actinide nuclei in a nuclear reactor. These processes comprise the manufacture of nuclear fuel elements, their irradiation in a reactor and the subsequent reprocessing of the irradiated fuel to recover fissile and fertile material.[11] There are also two closely associated processes which are not part of the cycle itself. The first is the extraction of fissile and fertile material from ore deposits and the second is the treatment and disposal of the wastes generated by the cycle, especially by the reprocessing stage. In order to place these processes in perspective it is useful to consider the complete lifespan of the actinide elements as summarized in Figure 1. Since their formation during stellar element synthesis and nuclear reactions in supernovae, most actinide isotopes have had time to decay to insignificant levels by radioactive processes. Only those isotopes with half lives approaching the age of the Universe are found in significant quantities on Earth. These are ^{238}U ($t_{1/2} = 4.47 \times 10^9$ y), ^{235}U ($t_{1/2} = 7.04 \times 10^8$ y) and ^{232}Th ($t_{1/2} = 1.405 \times 10^{10}$ y), of which only ^{235}U is fissile. Small amounts of other actinides, particularly neptunium, actinium, protactinium and plutonium, also occur naturally, either as a result of neutron capture in actinide bearing rocks or from radioactive decay processes. These elements are not of primordial origin and, although gram quantities of protactinium have been obtained by reprocessing uranium ore residues, they are usually best obtained by neutron irradiation of suitable target materials in a nuclear reactor.

During the Earth's history, geochemical processes have led to the segregation of the uranium and thorium present in the crustal rocks and to the formation of uranium ore deposits containing as much as a few percent uranium in some cases. If left in the ground this uranium and thorium would eventually decay to stable lead isotopes. However, if instead they are extracted and fed into a nuclear fuel cycle, their destruction may be accelerated and fission energy produced. Since each fission event libertates 208 MeV of energy, the potential energy stored in a fissile actinide represents some three million times that available from the combustion of a similar mass of fossil fuel. Natural uranium contains only 0.7% of fissile ^{235}U and in the form of metal or oxide cannot sustain a fission chain reaction. This results from the small fission cross section offered by the ^{235}U nucleus to the energetic 'fast' neutrons released during fission. A much higher ^{235}U concentration is necessary to maintain a fission chain under such circumstances. However, the fission cross section of ^{235}U is larger with respect to slow or 'thermal' neutrons. Thus if natural uranium is placed in a medium such as graphite, water or D_2O, which can act as a moderator and slow down, or thermalize, the fission generated neutrons, a chain reaction may be sustained. It is the application of this strategy which underlies the thermal reactor nuclear fuel cycle set out on the right hand side of Figure 1. Thus natural uranium, in the form of metal in the case of the older graphite moderated British Magnox ractor, or oxide in the D_2O moderated Canadian CANDU reactor, may sustain a fission chain reaction in a thermal reactor. Although it is possible to utilize natural uranium in this way, greater efficiencies in energy production may be achieved if a higher ^{235}U concentration is used in conjunction with a moderator. Consequently the newer British Advanced Gas Cooled Reactor (AGR) and the American Pressurized Water Reactor (PWR) systems, which are graphite and water moderated respectively, utilize fuels containing uranium enriched to 2.3% and 3.2% ^{235}U. These reactor systems thus require an additional enrichment stage between the uranium extraction process and the fuel fabrication stage.

During the irradiation of the fuel in the neutron flux of the reactor, two important processes are occurring. Firstly, the fissile ^{235}U nuclei are splitting to generate some 40 or so fission product elements (FPs). These all have different half-lives and some will have largely decayed at the time the fuel is discharged from the reactor. After three years the more important FPs remaining in irradiated PWR fuel are, in order of decreasing radioactive contribution to total fuel activity,[13] ^{137}Cs, ^{137m}Ba, ^{144}Pr, ^{144}Ce, ^{106}Ru, ^{106}Rh, ^{90}Sr, ^{90}Y, ^{147}Pm, ^{134}Cs, ^{154}Eu, ^{85}Kr, ^{125}Sb, ^{155}Eu, ^{125m}Te, ^{3}H, ^{151}Sm, ^{111m}Ag, ^{113m}Cd, ^{95}Nb, ^{123}Sn, ^{95}Zr, ^{99}Tc, ^{127}Te and ^{119m}Sn. Secondly, neutron capture reactions are occurring. One of these results in the formation of fissile ^{239}Pu from fertile ^{238}U according to Scheme 1. Some of the ^{239}Pu produced will also undergo fission, but ^{239}Pu may represent some 0.5% of the actinide content of the fuel discharged from the reactor. Neutron capture reactions also result in the formation of other plutonium isotopes along with some americium and curium.

$$^{238}U \xrightarrow{n,\gamma} {}^{239}U \xrightarrow[23 \text{ min}]{} {}^{239}Np \xrightarrow[2.3\,d]{\beta^-} {}^{239}Pu$$

Scheme 1

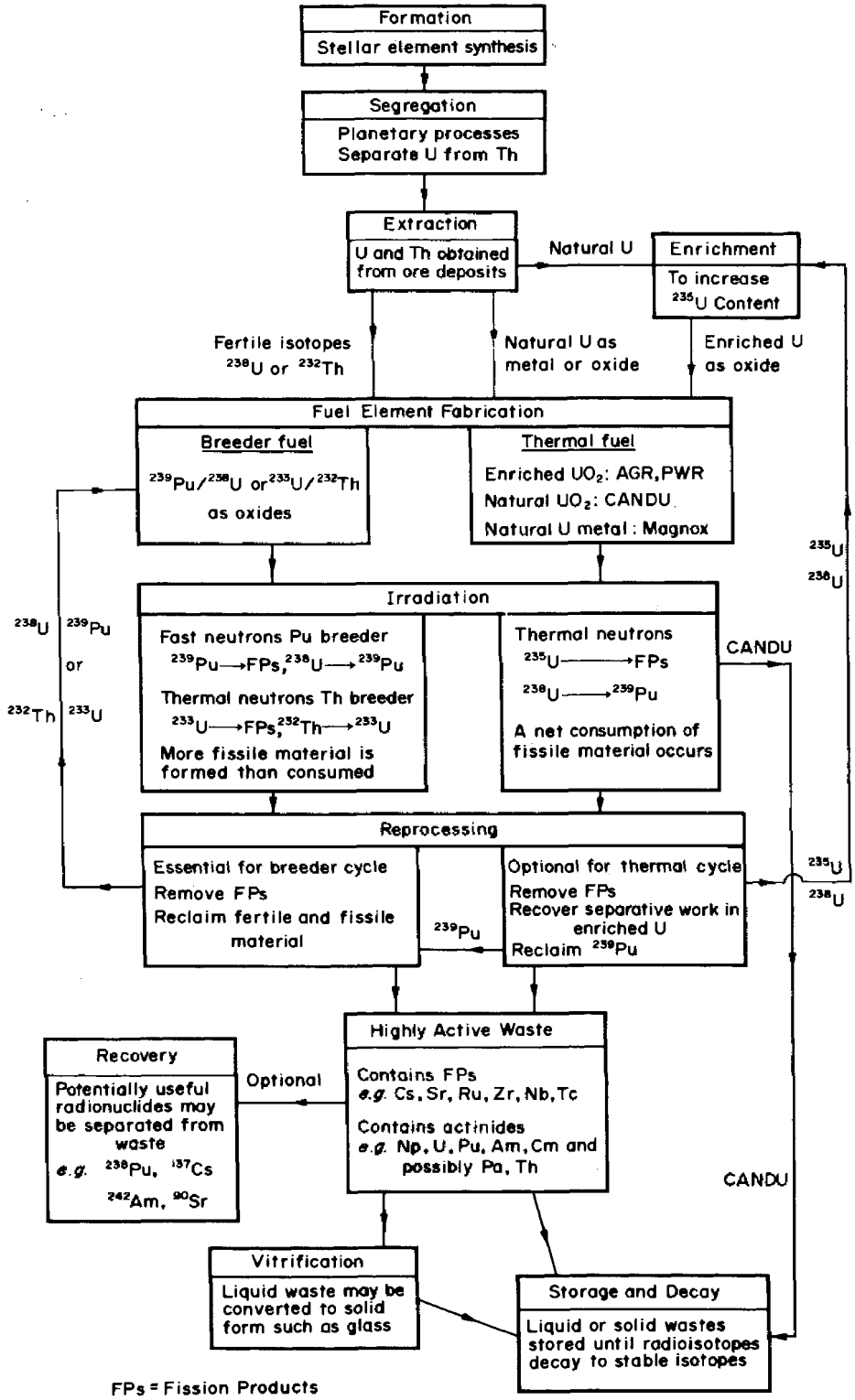


Figure 1 The actinide life cycle

It is processes of this second type which make possible the alternative 'breeder reactor' fuel cycle shown on the left side of Figure 1. If the excess neutrons emitted from the core of an operating fission reactor are absorbed in a surrounding 'blanket' of fertile ^{238}U, capture reactions will lead to the formation of ^{239}Pu. Thus it is in principle possible to generate more fissile material in the blanket than is consumed in the core. The use of natural uranium to produce plutonium in a breeder cycle of this type could increase the available fission energy by a factor of 50-60. However, to realize this goal conditions are needed which differ substantially from those found in a thermal reactor. The neutron capture, or 'breeding', process is more efficient when unmoderated fast' neutrons are used. Thus in order to optimize the 'breeding gain' of the reactor an unmoderated core is required. This in turn requires a much higher concentration of fissile material in the reactor core if a chain reaction involving fast neutrons is to be sustained. A fuel containing about 20% fissile material is necessary. A further feature of such a reactor system is the high energy density in its core during normal operation. This may be of the order of 0.5 MW dm^{-3} and the CO_2 or water coolants used in the AGR and PWR are not sufficiently good conductors of heat to transfer energy out of the core at the required rate. More effective coolants, such as liquid metals, are necessary, sodium being the metal of choice. It is this need for a liquid metal coolant and fast neutrons in an effective breeder system that gives reactors of this type the name Liquid Metal Fast Breeder Reactor (LMFBR). The breeder cycle thus involves the fabrication of both core and blanket fuel elements. The core contains ^{239}Pu as its fissile component while the blanket contains ^{238}U as its fertile component. After irradiation, both the blanket and core must be reprocessed to remove the fission products and recover the fissile ^{239}Pu and fertile ^{238}U for recycling through the reactor. In this way the ^{238}U in natural uranium can also be used as a source of fission energy. The $^{238}U/^{239}Pu$ breeder reactor cycle is under development in Britain, France and the USSR with prototype reactors operating in all these countries. An alternative breeder cycle involves ^{233}U and ^{232}Th as its fissile and fertile components as summarized in Scheme 2. This offers the advantage of a superior neutron yield of ^{233}U in a thermal reactor system. However, the 1.9 y half-life α-emitter ^{228}Th is also formed and presents a major problem in the reprocessing stage.[24] Such a cycle would allow the world's thorium reserves to be added to its uranium reserves as a potential source of fission power. However, the $^{232}Th/^{233}U$ cycle is unlikely to be developed in the near future owing to the more advanced state of the $^{238}U/^{239}Pu$ cycle and the current availability of uranium.

$$^{232}\mathrm{Th} \xrightarrow{n,\gamma} {}^{233}\mathrm{Th} \xrightarrow[22.3\ \mathrm{min}]{\beta^-} {}^{233}\mathrm{Pa} \xrightarrow[27.0\ \mathrm{d}]{\beta^-} {}^{233}\mathrm{U}$$

Scheme 2

In the case of the thermal cycle, fuel reprocessing is not essential. In the CANDU system, for example, the fuel is placed in secure long-term storage without reprocessing. However, this spent fuel still contains some unused ^{235}U, a substantial amount of ^{238}U and some fissile ^{239}Pu along with other actinides and the FPs. In the case of reactors using enriched fuels the final ^{235}U content may still be greater than in natural uranium. Since enrichment is an expensive energy intensive process, recovery of the separative work embodied in any increased ^{235}U content may provide an incentive for reprocessing. Also the plutonium recovered from the reprocessing of thermal reactor fuel may be incorporated into the breeder cycle. The final composition of the irradiated fuel will depend upon its initial fissile material content and the energy spectrum of the neutrons to which it has been exposed. It will also depend upon the extent to which the fuel has been irradiated, that is its 'burn-up'. The irradiation history of the fuel may then have a bearing on the process chemistry of any subsequent reprocessing stage.

The primary aim of the reprocessing stage is to remove neutron absorbing fission products which, if allowed to accumulate in the fuel, could impair reactor performance. However, since the actinide product streams from reprocessing must be accepted back into the enrichment or fuel fabrication processes to complete the cycle, extremely effective separation of the fuel from all FPs and higher actinides is necessary. The concentrations of plutonium and ^{106}Ru in the uranyl nitrate product from British Nuclear Fuels 'Thermal Oxide Reprocessing Plant' (THORP), for example, are required[11] to be respectively 5×10^8 and 1×10^8 less than in the irradiated fuel fed into the plant. These figures are known as decontamination factors, DF_{Pu} and DF_{Ru} in this case, and are normally defined in terms of the radioactivity of a fuel contaminant X measured in nuclear disintegrations per unit time as shown in equation (1). The magnitudes of these DF values illustrate the need for a process which can separate uranium, and plutonium, selectively from a mixture containing up to about 40 elements. The radioactive fission products and higher actinides separated from the fuel provide a potential source of useful radionuclides such as ^{137}Cs and ^{238}Pu. Further separation processes may thus be included to extract specific elements from the highly active

waste (HAW) produced by fuel reprocessing. Another important aim of the reprocessing stage is to convert the unwanted materials in this HAW to a form suitable for long-term storage. To this end it is desirable to combine all the radioactive wastes in one HAW stream. The FP activity in this stream will have decayed by a factor of 10^5 before levelling off after almost 10^3 y. However, it will be over 10^6 years before the actinides have decayed to a level where their radiotoxicity falls below that of the original ore had it been left in the ground. The secure storage of radioactive materials over such a timescale presents a major challenge to the nuclear industry. At present the most highly developed process for long-term HAW storage is vitrification. This involves the incorporation of the HAW into borosilicate glass blocks which are expected to provide a thermally stable leach-resistant matrix in which the FPs and actinides will remain immobilized over geological time scales.

$$DF_X = \frac{\text{Activity of X per unit mass of U in feed}}{\text{Activity of X per unit mass of U in product}} \quad (1)$$

Viewed in the context of the actinide lifespan, the nuclear fuel cycle involves the diversion of actinides from their natural decay sequence into an accelerated fission decay sequence. The radioactive by-products of this energy producing process will themselves ultimately decay but along quite different pathways. Coordination chemistry plays a role at various stages in this diversionary process, the most prominent being in the extraction of actinides from ore concentrate and the reprocessing of irradiated fuel. However, before considering these topics in detail it is appropriate to consider briefly the vital role played by coordination chemistry in the formation of uranium ore deposits.

65.2.1 The Geochemical Segregation of Uranium from Thorium

Uranium and thorium are not particularly rare metals. They occur to the extent of about 4 and 12 p.p.m. respectively in continental rocks as a whole.[24] The average Th:U ratio in the earth's crust is thus about 3, and not greatly different from the cosmological value[25] of 2.23. This suggests that these elements were not segregated to any major extent during primary differentiation and the formation of the molten planetary core. The electropositive nature and high oxygen affinities of uranium and thorium led to their appearance in the oxide and silicate components of the early rock forming system. However, the ionic charges and radii of U^{IV} and Th^{IV} are sufficiently different from those of the major metallic components of crustal rocks that they would largely be excluded from the rock lattice during crystallization. This led to their being mainly associated with minerals forming after the bulk of the rock had crystallized. In support of this general view, autoradiographic studies of granites have shown that most of their radioactivity is associated with microcrystalline inclusions and materials residing along grain boundaries within the rock mass.[26]

$$U^{4+} + 2H_2O \rightarrow UO_2^{2+} + 4H^+ + 2e^- \quad (2)$$

$$U^{III} \xrightarrow{-1.95\ V} U^{IV} \xrightarrow{0.08\ V} U^{V} \xrightarrow{-0.23\ V} U^{VI}$$

$$U^{IV} \xrightarrow{-0.07\ V} U^{VI}$$

Scheme 3

The release of uranium and thorium from minerals into natural waters will depend upon the formation of stable soluble complexes. In aqueous media only Th^{IV} is known but uranium may exist in one of several oxidation states. The standard potential for the oxidation of U^{4+} in water according to equation (2) has been re-evaluated[27] as $E^\circ = 0.273 \pm 0.005$ V and a potential diagram for uranium in water at pH 8 is given in Scheme 3.[28] This indicates that U^{III} will reduce water, while U^V is unstable with respect to disproportionation to U^{IV} and U^{VI}. Since the Earth's atmosphere prior to about 2×10^9 y ago was anoxic, and mildly reducing, U^{IV} would remain the preferred oxidation state in natural waters at this time. A consequence of this was that uranium and thorium would have exhibited similar chemistry in natural waters, and have been subject to broadly similar redistribution processes early in the Earth's history. Both U^{IV} and Th^{IV} are readily hydrolyzed in aqueous solutions of low acidity. A semiquantitative summary of the equilibrium constants for the hydrolysis of actinide ions in dilute solutions of zero ionic strength has been provided by Liljenzin and coworkers.[28] The results obtained for Th^{4+}, U^{4+} and UO_2^{2+} are summarized in Table 1. The tetracations of the oxidation state (IV) metals are the dominant species only below pH 1. Above pH 8 the monoanionic $M(OH)_5^-$ complexes are expected to be the dominant species in solution, although the bulk of the metal will have precipitated at this

Table 1 Equilibrium Constants for the Formation of Hydroxy Complexes at Zero Ionic Strength and 25 °C

Reaction	*Metal Ion M^z =*	*Estimated log K value*[a] Th^{4+}	U^{4+}	UO_2^{2+}
$M^z + OH^- \rightleftharpoons M(OH)^{z-1}$		10.8 ± 0.3	13.4 ± 0.4	8.1 ± 0.2
$M^z + 2OH^- \rightleftharpoons M(OH)_2^{z-2}$		22.2	(25.5 ± 0.8)	(17.2 ± 0.8)
$M^z + 3OH^- \rightleftharpoons M(OH)_3^{z-3}$		—	(36.6 ± 1.2)	(21 ± 2)
$M^z + 4OH^- \rightleftharpoons M(OH)_4^{z-4}$		40.1	(46.3 ± 1.6)	—
$M^z + 5OH^- \rightleftharpoons M(OH)_5^{z-5}$		—	54.0 ± 2.0	—
$M^z + OH^- \rightleftharpoons M_2(OH)^{2z-1}$		—	—	9.6 ± 5
$M^z + 2OH^- \rightleftharpoons M_2(OH)_2^{2z-2}$		21.9 ± 0.6	27 ± 3	22.4 ± 0.2
$M^z + 3OH^- \rightleftharpoons M_2(OH)_3^{2z-3}$		—	40 ± 4	—
$M^z + 4OH^- \rightleftharpoons M_2(OH)_4^{2z-4}$		—	52 ± 5	—
$M^z + 5OH^- \rightleftharpoons M_2(OH)_5^{2z-5}$		—	62 ± 6	—
$M^z + 4OH^- \rightleftharpoons M_3(OH)_4^{3z-4}$		—	—	44.2 ± 0.5
$M^z + 5OH^- \rightleftharpoons M_3(OH)_5^{3z-5}$		—	—	55 ± 1
$M^z + 8OH^- \rightleftharpoons M_4(OH)_8^{4z-8}$		90.9 ± 0.1	—	−22.4 ± 0.2
$M(OH)_4^{z-4}(solid) \rightleftharpoons M^z + 4OH^-$		−44.7	(−54 ± 2)	—
$M(OH)_2^{z-2}(solid) \rightleftharpoons M^z + 2OH^-$		—	—	−22.4 ± 0.2
$MO_2(solid) + 2H_2O \rightleftharpoons M^{4+} + 4OH^-$		−49.7	−57.8 ± 2	—

Values in parentheses were obtained by extrapolation.

pH. Below pH 6 a mixture of several hydroxy species would be formed. An investigation[29] of Th^{4+} hydrolysis in 0.1 M KNO_3 solution has indicated that, under these conditions, $Th(OH)^{3+}$, $Th_4(OH)_{12}^{4+}$ and $Th_6(OH)_{15}^{9+}$ were formed* with overall stability constants log $\beta = 2.98(0.007)$, 30.55(0.03) and 34.41(0.03) respectively, the estimated standard deviations being given in parentheses. No evidence for the formation of dinuclear species such as $Th_2(OH)_2^{2+}$ was found. The thermodynamic data available for uranium complexes have been critically evaluated by Langmuir[27] in order to predict the speciation of uranium in natural waters. In a model aqueous phase containing fluoride (2 p.p.m.), chloride (10 p.p.m.), sulfate (100 p.p.m.) and phosphate (1 p.p.m.), $U(OH)_5^-$ was the dominant species above pH 6 and below pH 3 only the fluoride complexes UF^{3+}, UF_2^{2+}, UF_3^+ and UF_4 were present. Between pH 3 and 6, $U(OH)_2^{2+}$, $U(OH)_3^+$, $U(OH)_4$ and $U(OH)_5^-$ were formed to varying extents, with $U(OH)_4$ predominating at pH 4. At low pH, fluoride ion plays a prominent role in the solubility of UO_2 in water at 25 °C. In the absence of F^- at pH 2 the total dissolved uranium concentration is 10^{-10} M, while the presence of 2 p.p.m. total fluoride increases this value to *ca.* 10^{-5} M. However, at pH 4–5 the effectiveness of F^- ceases and the dissolved uranium concentration reaches a minimum of 10^{-13} M. The uranium concentration then increases linearly with pH to about 10^{-9} M at pH 9.

The low solubilities of U^{IV} and Th^{IV} in natural waters of pH 4–7 would lead to their being transported mainly in the solid phase. That is either as components of the mineral lattice of resistate grains released during rock weathering, or as complexes adsorbed on soils or sediments and, in the case of thorium, on clay minerals.[26,30] The importance of the organic fractions of soils and sediments is illustrated by a study of the binding of Th^{IV} to humic and fulvic acids obtained from lake sediments.[31] The binding to humic acid was thought to occur at two sites, the first involving one carboxylate moiety and the second two carboxylates. The thermodynamic data for these systems are given in Table 2 and include positive entropy values two to three times the magnitude of those found for acetate or sulfate complexing of Th^{4+}. This was thought to indicate a higher degree of desolvation in the complexing of Th^{4+} by humic or fulvic acid. This may arise through the organic macromolecule providing regions of comparatively low dielectric constant around the binding sites.

Approximately 2×10^9 years ago the activities of photosynthetic algae wrought a dramatic change in the composition of the Earth's atmosphere through the release of large quantities of oxygen. Under these new conditions the widespread oxidation of U^{IV} to U^{VI} became possible in rocks and sediments exposed to the atmosphere. The formation of water soluble uranyl complexes could provide a powerful mechanism for the dissolution and aquatic transport of uranium and thus would lead to its geochemical segregation from thorium, for which no such oxidized species could form. In the U-O_2-H_2O system,[32] soluble uranium species are only formed at rather high or low pH values. However, in the presence of CO_2, soluble carbonate complexes are formed

* These species are solvated but to an unknown extent. In this chapter, metal complex formulae will only be written in square brackets when they represent discrete molecular species in which the metal coordination sphere is complete.

Table 2 Thermodynamic Data[a] for the Binding of Th^{IV} to Humic and Fulvic Acids[30]

	pH	*log β*	$-\Delta G$ (kJ eq^{-1})	ΔH (kJ eq^{-1})	ΔS (J eq^{-1} K^{-1})
Th(humate)	4.0	—	63.56 ± 0.06	32.6 ± 3.2	323 ± 10
	3.95	11.140 ± 0.013			
	4.60	12.027 ± 0.023			
	5.03	13.181 ± 0.038			
$Th(humate)_2$	4.0	—	92.23 ± 0.12	42.7 ± 3.3	453 ± 12
	3.95	16.168 ± 0.023			
	4.60	17.289 ± 0.043			
	5.03	18.434 ± 0.173			
Th(fulvate)	4.0	—	55.90 ± 0.18	18.9 ± 4.2	251 ± 44
	4.01	9.798 ± 0.029			
	5.00	10.824 ± 0.051			
$Th(fulvate)_2$	4.0	—	76.97 ± 0.33	46.4 ± 8.4	414 ± 30
	4.01	13.495 ± 0.056			
	5.00	15.073 ± 0.084			

[a] Data obtained at 25 ± 0.5 °C at ionic strength 0.1 M as $NaClO_4 + NaO_2CMe$.

which stabilize UO_2^{2+} in solution over a wide range of pH values.[32] Thus although hydrated UO_2^{2+} is only found in solution below pH 4 in the absence of CO_2, under a CO_2 partial pressure of 10^{-3}–10^{-1} bar at 25 °C soluble UO_2CO_3 forms in the region pH 4–5 with $[UO_2(CO_3)_2(H_2O)_2]^{2-}$ predominating between pH 5 and pH 11. Above pH 11, $[UO_2(CO_3)_3]^{4-}$ becomes the dominant species in solution. The rate of dissolution of uraninite, UO_2, in groundwater containing O_2 and CO_2 has been studied by Grandstaff and the empirical model given by equation (3) was proposed.[33] The rate of dissolution (mol d^{-1}) is given in terms of the specific surface area (SA cm^2 gm^{-1}) of the UO_2, the total dissolved carbonate concentration (a_{CO_2} mol dm^{-3}), the dissolved O_2 concentration (a_{O_2} p.p.m.), the mole fraction of non-uranium cations (mainly Th^{4+} and Pb^{2+}) present (N), the temperature (T K), the hydrogen ion activity (a_{H^+} mol dm^{-3}) and a retardation factor (R) to take account of the poisoning of UO_2 surfaces by organic matter. The proposed mechanism of dissolution involved the slow adsorption of O_2, followed by its splitting and surface migration to form hydrated UO_3 according to equations (4) and (5). Subsequent reactions of $UO_3 \cdot H_2O$ with bicarbonate according to equations (6) and (7) then afford $[UO_2(CO_3)_2(H_2O)_2]^{2-}$. One fast and one slow reaction were proposed to account for the first order dependence on a_{CO_2}. In order to account for the first order dependence of rate on a_{H^+} a hydration reaction of UO_2 was proposed as shown in equation (8). Subsequent ionization could then lead to the species given in equations (9) and (10). If only the protonated form of the hydrate could be involved in O_2 binding, a dependence on a_{H^+} would be expected.

$$\frac{-d[U]}{dt} = 10^{20.25}\, SA\, R^{-1}\, (10^{-3.38-10.8N})\, a_{CO_2}\, a_{H^+}\, a_{O_2} \exp(-7045/T) \quad (3)$$

$$UO_2 + O_2 \rightarrow UO_2 \cdot O_2 \quad \text{(slow)} \quad (4)$$

$$UO_2 + O + H_2O \rightarrow UO_3 \cdot H_2O \quad \text{(fast)} \quad (5)$$

$$UO_3 \cdot H_2O + HCO_3^- \rightarrow UO_2(CO_3)(H_2O)(OH^-) \quad \text{(slow)} \quad (6)$$

$$UO_2(CO_3)(H_2O)(OH)^- + HCO_3^- \rightarrow UO_2(CO_3)_2(H_2O)_2^{2-} \quad \text{(fast)} \quad (7)$$

$$UO_2 + H_2O \rightarrow UO(OH)_2 \quad \text{(surface)} \quad (8)$$

$$UO_2(OH)_2 \rightarrow UO_2(OH)O^- + H^+ \quad (9)$$

$$UO_2(OH)O^- \rightarrow UO_3 \cdot O^{2-} + H^+ \quad (10)$$

The speciation of dissolved uranium in groundwater has been modeled in a study of uranium oxide fuel dissolution.[34] The calculated E_h–pH diagram for a typical groundwater composition is shown in Figure 2.[34,35] This again shows the importance of carbonate complexes but also indicates that halide complexes of UO_2^{2+} and, under certain conditions, UO_2^+ may also be important contributors to the aqueous phase at low pH. The stability constants or uranyl carbonate and hydroxocarbonate complexes have been determined[36] and are summarized in Table 3. These results were thought to indicate that $(UO_2)_2(CO_3)(OH)_3^-$ was also important in the aquatic speciation of uranium. However, natural waters also contain silicate and phosphate ions. Although

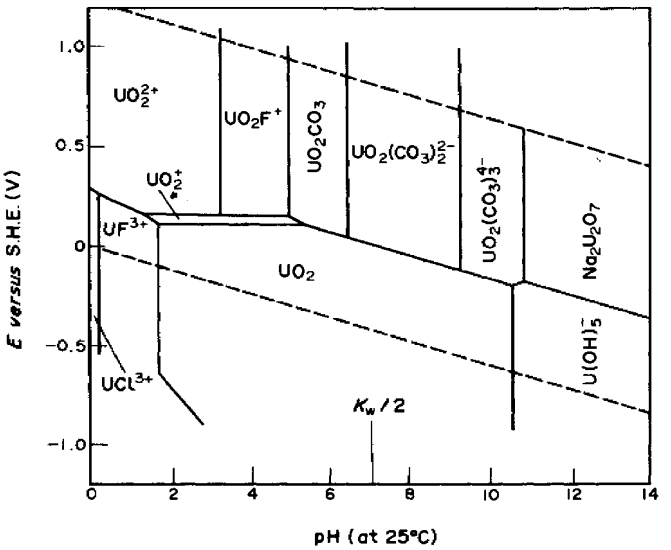


Figure 2 The E_h/pH diagram for uranium in a model groundwater containing 10^{-3} M total carbonate, 10^{-4} M sulfate, 8.6×10^{-4} M chloride and 10^{-4} M fluoride. (Reproduced from L. H. Johnson, D. W. Shoesmith, G. E. Lunansky, M. R. Bailey and P. R. Tremaine, *Nucl. Technol.*, 1982, **56**, 238, with the permission of the American Nuclear Society)

Table 3 Stability Constants for Uranyl Carbonate and Hydroxocarbonate Complexes[36]

Complex	$[UO_2(CO_3)_3]^{4-}$	$UO_2(CO_3)^{2-}$	$(UO_2)_2(CO_3)(OH)_3^-$	$(UO_2)_3(OH)_5^+$	$UO_2(OH)_2$
a,b,x[a]	1,3,0	1,2,0	2,1,3	3,0,5	2,0,2
$-\log^* \beta_{a,b,x}$[b]	31.21±0.05	19.19±0.29	18.63±0.08	16.19±0.16	5.89±0.37
Complex	$[UO_2(CO_3)_3]^{4-}$	$UO_2(CO_3)_2^{2-}$	UO_2CO_3	$(UO_2)_3(CO_3)_6^{6-}$	
u,t	1,3	1,2	1,1	3,6	
$\log \beta_{u,t}$[c]	21.3±0.2	16.6±0.2	9.5±0.2	53.4±0.8	

[a] a,b,x from:

$$a UO_2^{2+} + b CO_2 + c H_2O \rightleftharpoons [(UO_2)_a(CO_3)_b(OH)_{c-b}]^{2a-b-c} + (b+c)H^+$$

where $c-b=x$, $b+c=y$ and $2a-b-c=z$.

[b]
$$^*\beta_{a,b,x} = \frac{[(UO_2)_a(CO_3)_b(OH)_x^z][H^+]^y}{[UO_2^{2+}]^a \cdot pCO_2^b}$$

(for aqueous solutions containing 0.1 M ClO_4 and up to 2×10^{-3} M U).

[c]
$$\beta_{u,t} \text{ for } UO_2^{2+} + tCO_3^{2-} \rightleftharpoons UO_2(CO_3)_t^{(2t-2)-} \quad (u=1,\ t=1\text{-}3)$$

$$\beta_{u,t} \text{ for } 3UO_2^{2+} + 6CO_3^{2-} \rightleftharpoons (UO_2)_3(CO_3)_6^{6-} \quad (t=6,\ y=3)$$

(for aqueous solutions).

silicate complexation of UO_2^{2+} appears relatively unimportant,[27] the high formation constant[37] for $UO_2(HPO_4)_2^{2-}$ makes it a major component at intermediate pH, as shown in Figure 3. Thus at intermediate and high pH it is phosphate and carbonate complexes respectively which dominate the speciation of UO_2^{2+} in natural waters. At lower pH values, fluoride and, to a lesser extent, sulfate complexes may be present in addition to hydrated UO_2^{2+}.

This complexation of uranyl ion results in typical total dissolved uranium concentrations of between 0.1 and 10 p.p.b. in continental surface waters compared with a figure of 10^{-3}–10^{-2} p.p.b. for thorium. In aerated groundwaters, higher uranium concentrations of 10–100 p.p.b. are generally found. This difference in net water solubilities had led to major differences in the nature of commercial thorium and uranium reserves. Thorium is generally obtained from alluvial or sedimentary deposits formed in regions where heavy refractory minerals, weathered from a source rock, have been concentrated by mechanical processes. In contrast, the richest uranium deposits have formed in regions where chemical processes have immobilized and concentrated uranium from surface- or ground-water flowing through them. Furthermore, the less mobile thorium is found to be an essential compound of only six minerals, compared with over 70 for uranium. The major source mineral of thorium is monazite, a rare earth phosphate containing up to 10% Th as $LnPO_4$, where Ln represents a variety of metal ions but especially Ce^{III}, La^{III} and Y^{III} in combination with (Ca^{II}, Th^{IV}). Other important thorium minerals are thorianite, ThO_2, and thorite, $ThSiO_4$, both of which may also contain significant proportions of U^{IV}.[2]

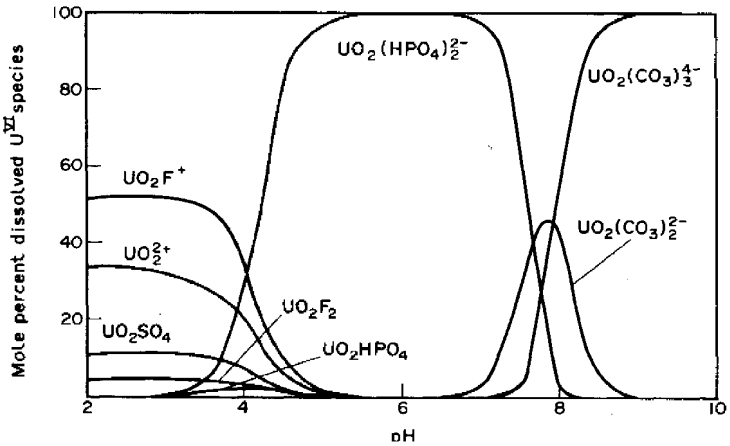


Figure 3 The distribution of uranyl complexes[27] as a function of pH at 25 °C with water containing 0.3 p.p.m. F^-, 10 p.p.m. Cl^-, 100 p.p.m. SO_4^{2-}, 0.1 p.p.m. PO_4^{3-}, 30 p.p.m. SiO_2 and with a partial CO_2 pressure of $10^{-2.5}$ bar

The aquatic transport of uranium as carbonate complexes is reflected in the formation of the uranyl carbonate minerals Rutherfordine, $UO_2(CO_3)$,[38] Leibigite, $Ca_2[UO_2(CO_3)_3]\cdot 10\text{–}11H_2O$,[39] and Andersonite, $Na_2Ca[UO_2(CO_3)_3]\cdot 6H_2O$.[40] Both natural and synthetic[41] UO_2CO_3 have similar structures which contain sheets of planar CO_3^{2-} ions. The uranyl groups have the normal *trans* dioxo configuration and occupy planar distorted hexagonal sites within these sheets. Each U^{VI} thus has a distorted hexagonal bipyramidal coordination geometry which involves two bidentate and two monodentate carbonate ligands. The $[UO_2(CO_3)_3]^{4-}$ ions in Leibigite, Andersonite and synthetically prepared $(NH_4)_4[UO_2(CO_3)_3]$[42] or $K_4[UO_2(CO_3)_3]$[43] also contain distorted hexagonal bipyramidal U^{VI} but in this case there are three bidentate carbonate ligands giving rise to discrete ions of the complex, as shown in Figure 4. These structures are similar to those found

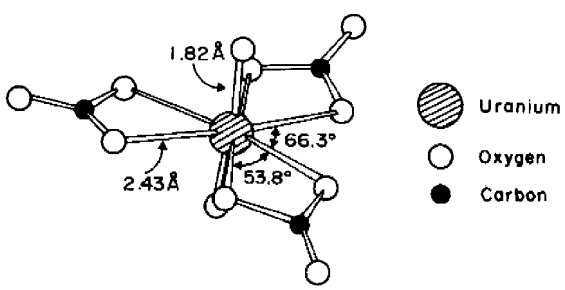


Figure 4 The structure of $[UO_2(CO_3)_3]^{4-}$ showing selected average bond lengths and angles[43]

in $Rb[UO_2(NO_3)_3]$[44] and $Na[UO_2(NO_3)_2(H_2O)_2]$[45] but contrast with the pentagonal bipyramidal coordination geometries found in $[UO_2(H_2O)_5]ClO_4\cdot 2H_2O$[46] and $[UO_2(OAc)_2(H_2O)]\cdot H_2O$[47] illustrated in Figure 5. The molecular structure of a $UO_2(CO_3)_2^{2-}$ complex has not been reported but

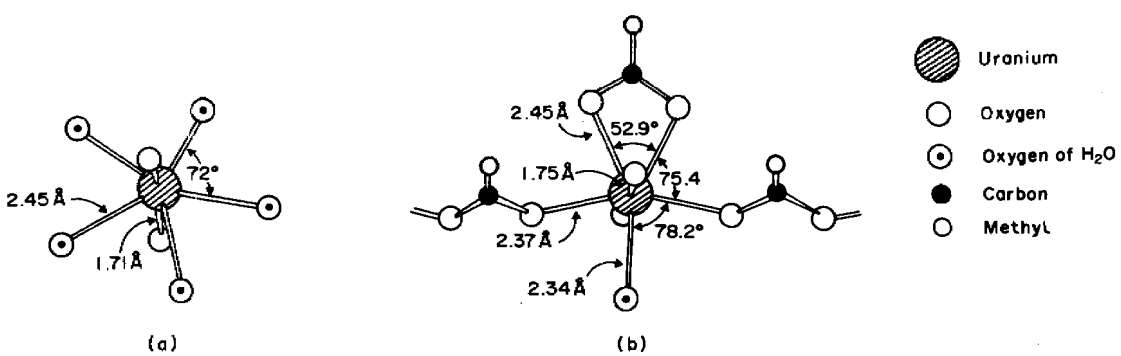


Figure 5 The structures of (a) $[UO_2(H_2O)_5]^{2+}$ and (b) $[UO_2(H_2O)(MeCO_2)_2]$ showing selected average bond lengths and angles. (Adapted from N. W. Alcock and S. Esperas, *J. Chem. Soc., Dalton Trans.*, 1977, 893, and R. Graziani, G. Bombieri and E. Forsellini, *J. Chem. Soc., Dalton Trans.*, 1972, 2059, with permission from the Royal Society of Chemistry)

studies in $NaHCO_3$ media[48] indicate that this complex will only be present in solutions which also contain substantial amounts of $[UO_2(CO_3)_3]^{4-}$.

Despite the importance of carbonate complexes in the aquatic transport of uranium, these carbonate minerals do not represent a major source of recoverable uranium. The chemical compositions of some of the more important uraniferous minerals are presented in Table 4 and their occurrence has been reviewed in several texts relating to the production of nuclear fuels.[2,49–51] The 1979 International Fuel Cycle Evaluation Conference defined the lowest production cost range for uranium as \$80 kg^{-1} or below including capital, direct mining and processing costs. Reasonably assured world reserves at this cost were estimated at 1.8×10^6 t. Out of this total some 84% was contributed by reserves in Australia, Canada, Namibia, the USA, South Africa and Niger. High-grade resources containing up to 0.2% uranium may be found in the sandstone deposits of the USA, Gabon and Niger. Overall, such sandstones account for about 35% of the uranium recoverable at low cost. A further 20% of low-cost reserves are in the form of veins, some being of hydrothermal origin, while an additional 15% are in the form of conglomerate deposits.[24]

Table 4 The Chemical Composition of Some Uranium Minerals[2,49]

Anion	*Mineral*	*Composition*
Oxides	Uraninite[a]	UO_2 } $(U^{IV}_{1-x}U^{VI}_{2})O_{2+x}$
	Pitchblende[a]	U_3O_8 }
	Gummite	$UO_3 \cdot nH_2O$
	Schoepite	$UO_2(OH)_2 \cdot H_2O$
	Brannerite	$(U,Ca,Fe,Th,Y)_3Ti_5O_{16}$
	Davidite	$(Fe,Ce,U)(Ti,Fe,V,Cr)_3(O,OH)_7$
Silicates	Coffinite	$U(SiO_4)_{1-x}(OH)_{4x}$
	Uranophane	$Ca(UO_2)_2(SiO_3)_2(OH)_2 \cdot 5H_2O$
Phosphates	Autunite	$Ca(UO_2)_2(PO_4)_2 \cdot 10\text{-}12H_2O$
	Torbernite	$Cu(UO_2)_2(PO_4)_2 \cdot 12H_2O$
	Monazite	$(Ce,Y,La)PO_4$ with Th and U
	Xenotine	YPO_4 with Th and U
Sulfates	Zippeite	$UO_2(SO_4)_2(H_2O) \cdot 8H_2O$
	Uranopilite	
Carbonates	Schroeklingerite	$NaCa_3(UO_2)(CO_3)_3SO_4F \cdot 10H_2O$
	Andersonite	$Na_2CaUO_2(CO_3)_3 \cdot 6H_2O \cdot 10H_2O$
	Liebigite	$Ca_2UO_2(CO_3)_3 \cdot 10\text{-}11H_2O$
	Rutherfordine	UO_2CO_3
Organics	Thucholite	Hydrocarbon matrix containing U, Th and rare earths
Vanadates	Carnotite	$K_2(UO_2)_2(VO_4)_2 \cdot 3H_2O$
	Tyuyamunite	$Ca(UO_2)_2(VO_4)_2 \cdot 7\text{-}10H_2O$

[a] Although uraninite is traditionally described as UO_2 and pitchblende as U_3O_8, both appear to represent a single mineral phase ranging from UO_2 in composition.[49]

The leaching of uranium from source rocks, and its subsequent mineralization, have been considered in detail by Hostetler and Garrels[32] and more recently by Langmuir.[27] The formation of uranyl minerals most commonly occurs in regions where evaporation can concentrate groundwater containing uranyl ions and complexing ligands such as vanadate, phosphate, silicate or arsenate, and where CO_2 concentrations are relatively low. The precipitation of UO_2^{2+} by vandate to give carnotite or tyuyamunite is an important fixation mechanism and leads to notable similarities between the distributions of uranium and vanadium. In the absence of vanadium, phosphate minerals such as autunite may form but, being more soluble, these are less abundant. The equilibrium constant K_{pv} given by equation (11) for the conversion of potassium autunite to carnotite according to equation (12) has been evaluated[27] as $10^{2.3}$ at 25 °C. The formation of soluble $UO_2(HPO_4)_2^{2-}$ means that, when phosphate and vanadate are both present, the total phosphate concentration must exceed that of vanadate by a factor of about 500 before autunite will precipitate in preference to carnotite. Similarly, very high silicate concentrations are required to precipitate uranophane in preference to autunite. The equilibrium constant for the conversion of uranophane to autunite according to equation (13) has been estimated[27] as $10^{22.6}$. In general the autunites and uranophanes are rarely precipitated from groundwater, except near to source rocks which have a low vanadium content but give rise to high groundwater phosphate or silicate concentrations. The optimum pH range for the precipitation of uranyl minerals is pH 5–8.5. This pH range also corresponds with the maximum sorption or uranyl on to organic materials, clays

and metal oxohydroxides. At higher pH the formation of carbonate complexes or species such as $(UO_2)_3(OH)_5^+$ leads to dissolution. At lower pH, UO_2^{2+} or its complexes with fluoride or sulfate dissolve. Uranium minerals, including carnotite, are most stable, and thus least soluble, under low partial pressures of CO_2. This in regions where carbonated groundwaters approach the land surface, and equilibrate with a lower atmospheric CO_2 content, mineral deposition will be favoured.

$$K_{pv} = [H_2PO_4^-]/[H_2VO_4^-] = 10^{2.3} \quad (11)$$

$$K_2[(UO_2)_2(PO_4)_2] + 2H_2VO_4^- \rightarrow K_2[(UO_2)_2(VO_4)_2] + 2H_2PO_4^- \quad (12)$$

$$Ca[(UO_2)_2(SiO_3OH)_2] + 2H_2PO_4^- + 2H^+ \rightarrow Ca[(UO_2)_2(PO_4)_2] + 2H_4SiO_4 \quad (13)$$

The structures of several uranyl minerals have been investigated using X-ray techniques. Carnotite was found[52,53] to have a similar structure to $Cs_2[(UO_2)_2(V_2O_8)]$, which contained infinite sheets of formula $[(UO_2)_2(V_2O_8)]_n^{2n-}$ separated by Cs^+ ions. The uranium had a distorted pentagonal bipyramidal coordination geometry in which a monodentate and two bidentate $[V_2O_8]^{6-}$ ligands contributed to an equatorial belt of five oxygens, as shown schematically in Figure 6. The

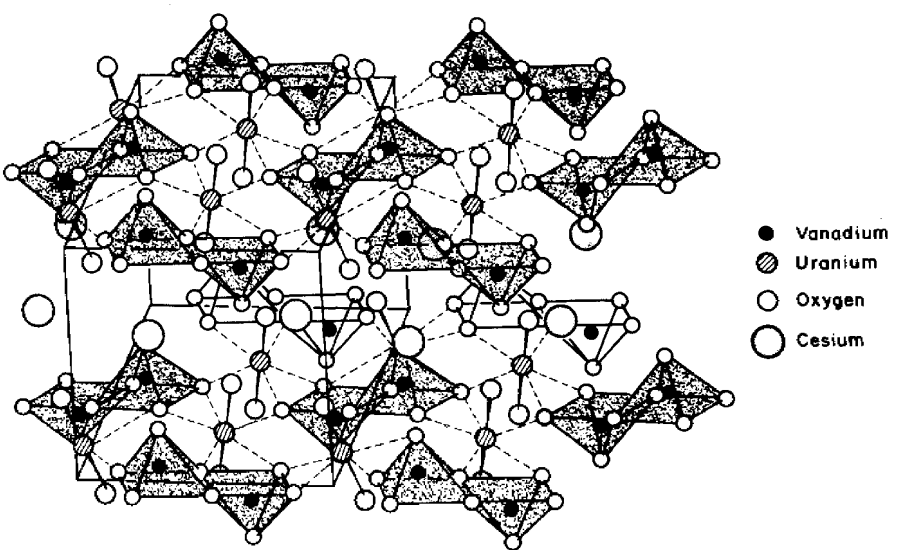


Figure 6 The uranium environment in carnotite (Reproduced from M. Ross, H. T. Evans and D. E. Appleman, *Am. Mineral.*, 1964, **49**, 1603, with permission from the Mineralogical Society of America)

$[V_2O_8]^{6-}$ ions were formed from two distorted square pyramidal $[VO_5]^{3-}$ units sharing an edge. The structure of meta-autunite, $Ca[(UO_2)_2(PO_4)_2]\cdot 8H_2O$, was related[54] to that of a meta-torbernite, $Cu[(UO_2)_2(PO_4)_2]\cdot 6H_2O$, which contained sheets of formula $[UO_2(PO_4)]_n^{n-}$. These were separated by planar $[Cu(OH_2)_4]^{2+}$ units which were also involved in a network of hydrogen bonds. In this case the uranium was in an octahedral coordination environment resulting from the *trans* oxo ligands and a square of oxygen atoms derived from four monodentate PO_4^{3-} ligands. The silicate mineral uranophane, $Ca[H_2(UO_2)_2(SiO_4)_2]\cdot 5H_2O$, like carnotite contained[55,56] uranium in a distorted pentagonal bipyramidal geometry, the equatorial belt of five oxygens being derived from one bidentate and three monodentate SiO_4^{4-} ligands as shown in Figure 7. The mineral structure contained sheets of formula $[(UO_2)_2(SiO_4)_2]_n^{4n-}$ linked through a network of hydrogen bonds and Ca—O interactions.

Another major processs involved in uranium mineral formation is the reduction of uranyl complexes to U^{IV} species of low solubility. This process may occur in regions where uraniferous groundwater passes into a zone of low E_h. The E_h-pH diagrams[27] for the $U\text{-}O_2\text{-}CO_2\text{-}H_2O$ and $K\text{-}U\text{-}V\text{-}O_2\text{-}H_2O\text{-}CO_2$ systems at 25 °C are presented in Figures 8 and 9. These indicate that, in the presence of vanadium, carnotite will precipitate between pH 5 and 8 even under oxidizing E_h conditions. However, in the absence of vanadium, insoluble UO_2 or U_4O_9 are only formed when the E_h falls below about 200 mV. Reducing conditions of this type may result from mixing with anoxic groundwater containing reducing agents such as Fe^{2+} or dissolved H_2S. Equations (14)

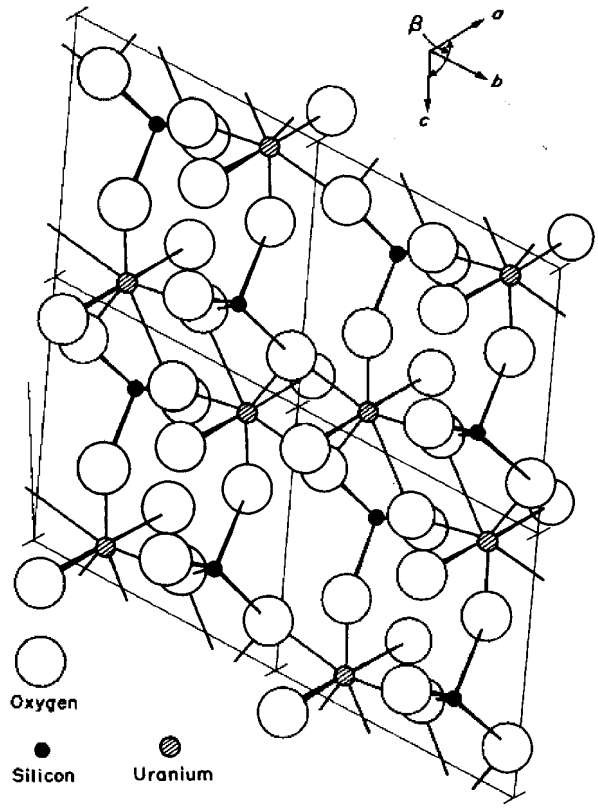


Figure 7 The uranium environment in uranophane. (Reproduced from D. K. Smith, J. W. Garner and W. N. Lipscomb, *Am. Mineral.*, 1957, **42**, 594, with permission from the Mineralogical Society of America)

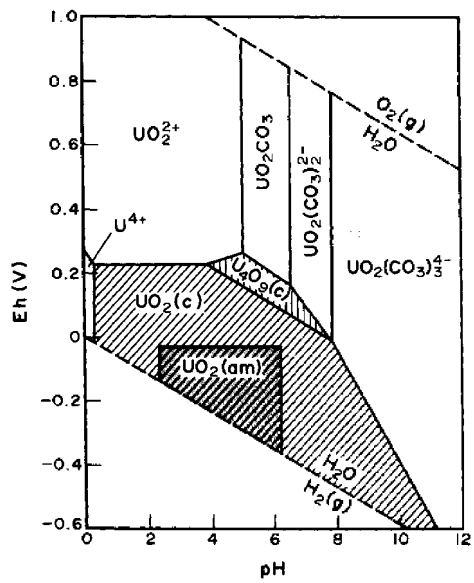


Figure 8 The E_h/pH diagram for the $U/O_2/CO_2/H_2O$ system at 25 °C with a partial CO_2 pressure of 10^{-2} bar.[27] Solid-solution boundaries are drawn at 10^{-6} M dissolved uranium species; UO_2am = amorphous UO_2

and (15) exemplify the formation of uraninite at pH 8 by such a process. The evolution of CO_2 and the formation of stable $Fe(OH)_3$ (solubility product = $10^{-38.5}$) or SO_4^{2-} would serve to drive these reactions to completion. Another mechanism for the formation of U^{IV} minerals is provided

$$[UO_2(CO_3)_3]^{4-} + 2Fe^{2+} + 3H_2O \rightarrow UO_2 + 2Fe(OH)_3 + 3CO_2 \quad (14)$$

$$4[UO_2(CO_3)_3]^{4-} + HS^- + 15H^+ \rightarrow 4UO_2 + SO_4^{2-} + 12CO_2 + 8H_2O \quad (15)$$

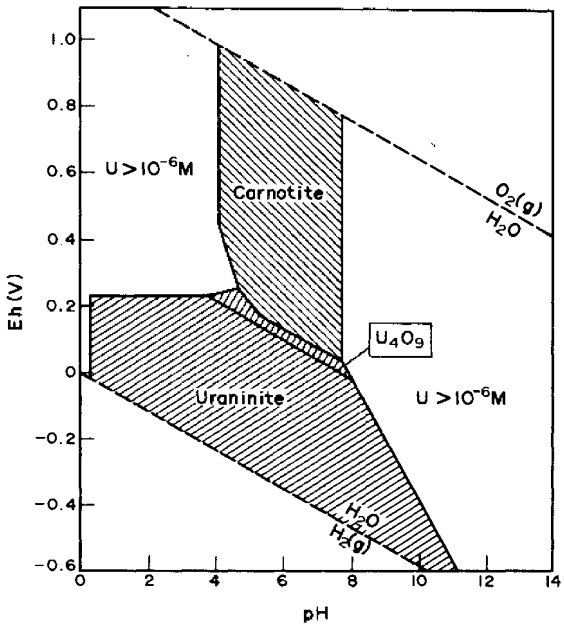


Figure 9 The E_h/pH diagram for the K/U/V/O_2/H_2O/CO_2 system[27] at 25 °C with 10^{-3} M K^+ and 10^{-6} M total uranium at solid solution boundaries and at a CO_2 partial pressure of 10^{-2} bar

Table 5 Thermodynamic Data for the Binding of Uranyl to Humic Acid[58]

Aqueous medium	*Complex*[a]	$\log \beta_i$	ΔG_i^+ (kJ eq^{-1})	ΔH_i^+ (kJ eq^{-1})	ΔS_i^+ (J eq^{-1} K^{-1})
Fresh[b]	UO_2(humate) $i=1$	5.11 ± 0.02	−29.2 ± 0.1	−2.7 ± 0.4	89
Fresh[b]	UO_2(humate)$_2$ $i=2$	8.94 ± 0.03	−51 ± 0.2	+8 ± 4	200
Sea[c]	UO_2(humate) $i=1$	7.6	—	—	—
Sea[c]	UO_2(humate)$_2$ $i=2$	11.5	—	—	—

[a] Humic acid of 4.2 meq g^{-1} ionizable acid content.
[b] Fresh water containing $\leq 10^{-8}$ M UO_2^{2+}, 8.4×10^{-3} eq dm^{-3} humic acid at pH 4.04 with 0.09 M $NaClO_4$ + 0.01 M glycollic acid.
[c] Seawater containing $\leq 10^{-8}$ M UO_2^{2+}, 10^{-5} eq dm^{-3} humic acid at pH 8.

by the contact of dissolved UO_2^{2+} with decaying organic matter which has become anaerobic. A dramatic, though rather special, example of this effect is provided by the formation of uranium logs.[57] These arise from contact between uranium bearing groundwater and decaying plant remains buried in a host sediment. Fossilized logs may then form which represent small, but very rich, sources of uranium. The formation of such deposits may involve the binding of uranyl ions to organic materials prior to reduction. A study[58] of the binding of UO_2^{2+} to humic acid has indicated the conditions under which adsorption to organic material might be favoured. Both 1:1 and 2:1 humic acid-uranyl complexes were found to form with the stability constants shown in Table 5. In groundwater of pH 6 containing 10^{-8} eq dm^{-3} humic acid it was predicted that the bulk of the UO_2^{2+} would be bound to humic acid. However, competitive complexation by carbonate has a major influence on this system so that, in seawater containing 10^{-5} M carbonate at pH 8 and 10^{-5} eq dm^{-3} humic acid, the UO_2^{2+} would largely be present in the form of carbonate complexes. Once fixed by binding to organic substances, UO_2^{2+} may either be desorbed, as a result of a change in pH or an increase in carbonate concentration, or undergo reduction resulting in the formation of uranium(IV) minerals,

A good example of the redistribution of uranium through weathering of a source rock, oxidative leaching of the released uraniferous minerals and subsequent reductive fixation of the uranium from surface waters, is provided by the formation of ore bodies in the Oklo region of Gabon in Africa.[59] In this instance, sufficiently rich uranium deposits were formed such that a uranium fission chain reaction occurred naturally in what has become known as the 'Oklo phenomenon'.[60,61] Early in the Earth's history the region surrounding the Oklo site was a vast watershed of igneous rock. The rainwater from the then oxygen deficient atmosphere gradually eroded away the rock

surfaces, preferentially releasing the intergranular material enriched in U and Th. This material was washed into the evolving network of streams where it accumulated, along with other debris from the weathering process, in the conglomerate sediments of the stream beds. These may have formed placer deposits similar to those in which gold and low-grade Precambrian uranium ores are still found today.

Around 2×10^9 years ago the appearance of oxygen in the atmosphere heralded the start of the process which would complete the transfer of U from a large area of low abundance to a small area of high abundance. The increasingly oxygenated water flowing in the streams dissolved the uranium which had accumulated in the stream beds and carried it down through the river system towards the ocean. At the coast the river dispersed over a swampy delta region of accumulated sediments well covered by vegetation. Conditions here were ideal for the reconcentration of the uranium which had once occupied such a large area and was now passing through this small region. The decaying vegetation in the delta sediments formed an anaerobic ooze rich in organic matter where the activities of microorganisms contributed to the production of reducing conditions. The U^{VI} entering the delta became entrapped in these oozes by adsorption or complexation and was then reduced to U^{IV} which became fixed in the sediments as they were further buried and eventually covered by sandstones.

Later, as the granite to the west of these deposits was uplifted and tilted, the U-rich sandstones became fractured and fissured, allowing some localized redistribution of uranium as a result of water circulation within the fissure system. At this stage the sediments were still buried sufficiently deeply for the circulating groundwater to be anaerobic. Only in recent times have the deposits come close enough to the surface for aerobic groundwater to reach them and begin redissolving the uranium present.

The shorter half life of ^{235}U, compared with that of ^{238}U, meant that at this time, *ca.* 1.8×10^9 y ago, natural uranium contained some 3% ^{235}U rather than its current level of 0.7%. Thus, in regions of the ore body where uranium concentrations greater than 10% were present in seams over 0.5 m thick, there was sufficient fissile material for the moderating effect of percolating groundwater to lead to a fission chain reaction. When the heat released was sufficient to boil the water and expel it, the moderating effect would be lost, so that the reactor zone would cycle between critical and subcritical conditions depending upon its water content. It has been estimated that the principal reactor zone at Oklo must have operated in this way for at least 1.5×10^5 years at a power level between 10 and 100 kW.

The discovery of a natural fission reactor such as this is not of purely academic interest; it also provides a unique opportunity for an empirical study of the behaviour of radionuclides in the ground over geological timescales. The events in the reactor zone at Oklo produced fission products and higher actinides. The subsequent migration of these elements from their site of formation has been the subject of detailed study[58] because of its implications for the disposal of high-level radioactive waste by land burial. In general the elements studied behaved according to predictions based on their known geochemistry and E_h-pH diagrams. The lanthanides, Y, Zr, Nb, Rh, Sn, Pu, Np and Am were expected to behave in a broadly similar manner to U^{IV} and to be retained in the uraninite deposit. This was found to be the case and the distribution of ^{235}U, as a daughter of ^{239}Pu, indicated that Pu had been immobilized for times comparable with its 24.4×10^3 y half life. The elements Ag, Tc, Ru, In, Sb, Te, Bi and Pd were expected to be retained as sulfides or carbonates but Bi, Pb, Tc and Ru did exhibit some local redistribution and a greater tendency to migrate than was predicted. The alkali and alkaline earth metals along with Cd and Mo were expected to migrate and this was bourne out by the site investigations. Thus it may be concluded that a study of the geochemistry of the actinides is contributing, not only to the identification of sources of material for use in the nuclear fuel cycle, but also to our understanding of the problems associated with disposing of wastes from the cycle.

65.2.2 The Recovery of Uranium and Thorium from Ores

65.2.2.1 Uranium

Although individual veins or grains of uraniferous minerals in ores may contain high uranium concentrations, approaching pure U_3O_8 in some cases, the overall uranium concentration in a commercially viable ore deposit will typically lie between 0.1 and 0.3% by weight. In order to reduce shipping costs and to provide an ore concentrate containing 60–70% uranium and acceptable for final refinement, it is usual for some processing of the ore to be carried out near

the mining site. The means by which a uranium concentrate may be prepared from the ore have been reviewed[49,50,62] and discussed at international symposia.[63–66] Figure 10 summarizes the main stages of the process. After removal from the ground the ore is often subjected to mechanical mineral dressing processes, such as grinding and froth flotation, in an attempt to concentrate the uranium rich components. However, in order to obtain a uranium concentrate containing up to 70% uranium a chemical treatment is essential. The chemistry of uranium milling has been reviewed by Svenke and coworkers,[67] and more recently by Hardy.[68] After the mineral dressing stage the ore is subjected to a chemical leaching treatment to dissolve the uranium. Sulfuric acid is usually chosen for this purpose, being less corrosive in dilute solution and less expensive than nitric or hydrochloric acids. However, some ores contain sufficient acid consuming components, carbonate salts for example, to make this approach uneconomic, and an alkaline leach may then be used. Unless the ore contains a high recoverable vanadium concentration, alkaline leaching would usually be preferred when a calcite content of over 8% is encountered or where the acid consumption exceeds 70–100 kg t^{-1} of ore. In either case the uranium is dissolved as U^{VI} so that oxidation of any U^{IV} present in the ore will be necessary for optimum recovery.

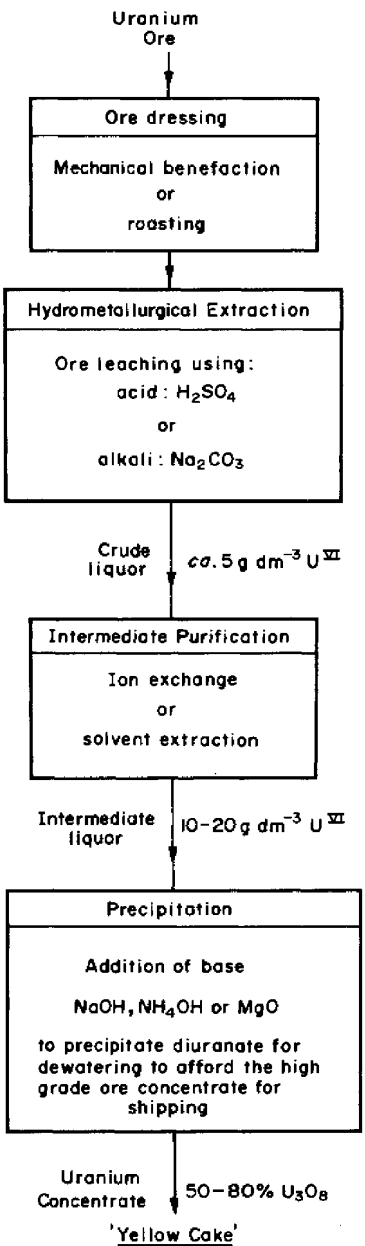


Figure 10 Outline flowsheet for the production of 'yellow cake' from uranium ore

(i) Alkali leaching

The alkali leaching process utilizes the high stability of soluble $[UO_2(CO_3)_3]^{4-}$ as a means of selectively dissolving uranium from the ore. This process has the advantage of allowing a comparatively pure uranium product to be precipitated directly from the leach liquor. The process solutions are also relatively noncorrosive. However, they are less efficient in removing uranium from the ore than acids. Consequently, finely ground feedstocks and leach liquor recycling in a closed circuit are necessary. In some cases, elevated temperature and pressure are also used to enhance the uranium recovery. Bicarbonate is added to the leaching solution to suppress hydroxyl ion concentrations according to equation (16), and to prevent the precipitation of uranyl hydroxide complexes. The finely divided ore is typically contacted with a solution containing 30–60 g dm^{-3} Na_2CO_3 and 5–15 g dm^{-3} $NaHCO_3$ at pH 9–10.5. Air is used as an oxidant for any U^{IV} present and the dissolution reactions which occur are summarized in equations (17) and (18). The rate of UO_2 oxidation has been found[69] to be proportional to the UO_2 surface area and the square root of the O_2 partial pressure. The reaction was thought to proceed *via* the rapid adsorption of O_2 on to the surface of UO_2 particles to give $UO_2{\cdot}O$ initially. This material is then more slowly converted to UO_3 on the surface.

$$HCO_3^- + OH^- \rightleftharpoons CO_3^{2-} + H_2O \quad (16)$$

$$UO_2 + \tfrac{1}{2}O_2 + 3CO_3^{2-} + H_2O \rightarrow UO_2(CO_3)_3^{4-} + 2OH^- \quad (17)$$

$$UO_3 + 3CO_3^{2-} + H_2O \rightarrow UO_2(CO_3)_3^{4-} + 2OH^- \quad (18)$$

However, more recent studies of UO_2 dissolution in groundwater were interpreted as showing the slow adsorption of O_2 followed by rapid UO_3 formation.[33] It has also been found[70] that uranium leaching rates increase with increasing solution H_2CO_3 concentration. This led to the proposal that H_2CO_3 could also adsorb on UO_2 and that subsequent reactions on the surface involving UO_3 would lead to the soluble $[UO_2(CO_3)_3]^{4-}$ complex as shown in equations (19)–(21). The oxidation of UO_2 to UO_3 was thought to be the rate determining step in the oxidation. However, it should be noted that electrochemical studies of the dissolution of UO_2 from reactor fuel suggest that the rate of reaction of O_2 with UO_2 to give U_2O_5 is sufficiently rapid to be diffusion controlled.[32] Direct reaction of the $UO_2{\cdot}O$ adsorbate with dissolved species was also proposed[69] as a dissolution mechanism, as shown in equations (22)–(26). However, such a mechanism would appear to be inconsistent with the finding that the formation of $UO_2(CO_3)_2^{2-}$ appears to proceed at a rate proportional to the surface UO_3 concentration. More recent work[71] has indicated that faster UO_2 dissolution in $(NH_4)_2CO_3$ can be achieved by using H_2O_2 as the oxidant, in place of O_2. The peroxy complex $[UO_2(O_2)(CO_3)_2]^{4-}$ has been identified in a study of the reaction of uranyl carbonate with anionic ligands,[72] but it is not clear whether such a species is formed during the UO_2 dissolution reaction. Usually a catalyst such as cuprammonium ion is added to accelerate the oxidation of UO_2 by air. During the leaching process, ore components such as sulfate and sulfide may contribute to carbonate consumption and, if elevated temperatures are used, acidic species such as silica or alumina can react to form bicarbonate.

$$UO_2(\text{surface}) + H_2CO_3(\text{solution}) \rightarrow UO_2{\cdot}H_2CO_3 \ (\text{surface}) \quad (19)$$

$$UO_2{\cdot}H_2CO_3 + UO_3 \rightarrow UO_2{\cdot}CO_3{\cdot}H_2O + UO_2 \ (\text{fast}) \quad (20)$$

$$UO_2{\cdot}CO_3{\cdot}H_2O + 2CO_3^{2-} \rightarrow [UO_2(CO_3)_3]^{4-} + H_2O \ (\text{fast}) \quad (21)$$

$$UO_2{\cdot}O + 2CO_3^{2-} + H_2O \rightarrow UO_2(CO_3)_2^{2-} + 2OH^- \ (\text{slow}) \quad (22)$$

$$UO_2{\cdot}O + 2HCO_3^- \rightarrow UO_2(CO_3)_2^{2-} + H_2O \ (\text{slow}) \quad (23)$$

$$UO_2{\cdot}O + CO_3^{2-} + HCO_3^- \rightarrow UO_2(CO_3)_2^{2-} + OH^- \ (\text{slow}) \quad (24)$$

$$UO_2(CO_3)_2^{2-} + HCO_3^- \rightleftharpoons [UO_2(CO_3)_3]^{4-} + H^+ \ (\text{fast}) \quad (25)$$

$$UO_2(CO_3)_2^{2-} + CO_3^{2-} \rightleftharpoons [UO_2(CO_3)_3]^{4-} \ (\text{fast}) \quad (26)$$

The recovery of uranium from the leach liquor is effected either by acidification to about pH 6 to liberate CO_2 or, more usually, by addition of hydroxide to precipitate diuranate, as shown in equation (27). In this latter case the pH is maintained at about 11. The species present in 0.055 M U^{VI} solutions, acidified to pH 4.56 under 1 bar CO_2 pressure, have been summarized[73] in a study of the reactive ion exchange adsorption of uranyl nitrate on to a bicarbonate loaded anion

exchange resin. These are shown in Table 6. The effect of ionic strength on the first hydrolysis constant of UO_2^{2+} in perchlorate media has also been described.[74] In another study of the effect of pH on carbonate complexation of UO^{2+}, species having the formulae $UO_2(CO_3)(H_2O)$, $(UO_2)_3(CO_3)(OH)_3(H_2O)^+$ and $(UO_2)_{11}(CO_3)_6(OH)_{12}(H_2O)_6^{2-}$ were identified, the latter appearing close to the pH at which precipitation occurred.[75] The solid state structure of another trinuclear uranyl complex, $[(UO_2)_3(\mu^3O)(OH)_3(H_2O)_6]NO_3\cdot 4H_2O$, has been reported recently.[76] This contained a triangular array of UO_2^{2+} groups linked by a triply bridging oxygen atom and three edge bridging OH^- ligands. Similar structural features may arise in other trinuclear uranyl complexes formed during precipitation reactions.

$$2Na_4[UO_2(CO_3)_3]+6NaOH \rightarrow Na_2U_2O_7+6Na_2CO_3+3H_2O \quad (27)$$

$$2NaOH+CO_2 \rightarrow Na_2CO_3+H_2O \quad (28)$$

$$Na_2CO_3+CO_2+H_2O \rightarrow 2NaHCO_3 \quad (29)$$

$$6NaHCO_3+Na_2U_2O_7 \rightarrow 2Na_4[UO_2(CO_3)_3]+3H_2O \quad (30)$$

After removal of the diuranate product, an ore concentrate known as 'yellowcake', the barren leach liquor is treated with CO_2 to regenerate HCO_3^- and redissolve any residual diuranate, as shown in equations (28)–(30), before it is recycled. The selectivity of the carbonate leaching process may allow an acceptably pure uranium concentrate to be obtained without the need for additional purification stages. In such cases the yellowcake will normally be subjected to dewatering and calcining to provide a higher density product prior to being transported to the refiner. Although this alkali leaching process offers certain advantages, it is acid leaching which offers the more efficient uranium recovery and which now provides the bulk of the uranium utilized in the nuclear industry.

Table 6 Speciation of U^{VI} (0.055 M) at pH 4.56 under 1 bar CO_2[73]

Species	*Concentration* (M)	*Stability constant log K*
$(UO_2)_3(OH)_5^+$	4.6×10^{-2}	−16.2
$(UO_2)_2(OH)_2^{2+}$	6.5×10^{-3}	−6.0
$UO_2(CO_3)$	2.1×10^{-3}	9.16
UO_2^{2+} (aquated)	1.6×10^{-3}	—
$[UO_2(CO_3)_3]^{4-}$	3.2×10^{-9}	21.4

(ii) Acid leaching

In the acid leaching process the finely divided uraniferous ore is contacted with acid, usually sulfuric acid, in the presence of added oxidants such as MnO_2 or $NaClO_3$. It is not, in fact, these reagents which oxidize the U^{IV} in the ore, but the Fe^{III} normally present, and which is converted to Fe^{II} according to equation (31). The oxidizing agents then reoxidize the Fe^{II} back to Fe^{III}, completing the cycle. A minimum iron concentration of 0.5 g dm^{-3} is required for this purpose. The U^{VI} present in the ore is converted directly to UO_2^{2+} according to equation (32) and subsequent complexation reactions with SO_4^{2-} form soluble uranyl species according to equations (33) and (34). Thermodynamic data[77] for the formation of uranyl sulfate complexes are given in Table 7. Excess acid is necessary to maintain a sufficiently low pH to prevent the precipitation of uranyl complexes with other anions in the leach solution. Between pH 3.5 and pH 6.0, carbonate and hydroxide complexes of UO_2^{2+} precipitate from sulfuric acid solutions and, if phosphate or arsenate are present, pH values below 1.9 and 1.3 respectively are needed to avoid precipitation. Typically a sulfate leach liquor may contain aquated UO_2^{2+} and $UO_2(OH)(SO_4)^-$ along with the sulfate complexes given in equations (33)–(35). However, $UO_2(SO_4)_2^{2-}$ is the dominant species in these solutions, which typically contain 0.5–1.5 g dm^{-3} uranium and 0.15 M sulfate. The solid state structures of a number of uranyl sulfate complexes have been reported in recent years, including $M_2[UO_2(SO_4)_2(H_2O)_2]$ (where $M^+ = NH_4^+$,[78] Rb^+[79] or K^+[80]), $UO_2SO_4\cdot 2.5H_2O$,[81] $UO_2SO_4\cdot 3.5H_2O$,[82] UO_2SO_4,[83] $(UO_2SO_4)_2\cdot 7H_2O$[84] and $K_4[UO_2(SO_4)_3]$.[85] Pentagonal bipyramidal seven-coordination of the uranium is most commonly found in these systems, with the *trans* dioxouranyl group being surrounded by an equatorial belt of five oxygens derived from the other

Table 7 Thermodynamic Data[a] relating to the Formation of Uranyl Sulfate Complexes[77]

$UO_2(SO_4)_n^{(2n-2)-}$	$n=1$	$n=2$
$\log K_n$	1.81	0.95
$\Delta G_n°$ (kJ mol^{-1})	−10.3	−5.4
$\Delta H_n°$ (kJ mol^{-1})	18.2	16.9
$\Delta S_n°$ (J mol^{-1} K^{-1})	96	75

[a] Ionic strength = 1, 25 °C.

ligands. The nonselective nature of the acid leaching process results in various other metals being dissolved from the uranium ore. If an acceptably pure uranium concentrate is to be produced by precipitation from the leachate, the uranium must first be separated from these other contaminants in an intermediate purification stage. This may involve the use of either ion exchange or solvent extraction processes.

$$UO_2 + 2Fe^{3+} \rightarrow UO_2^{2+} + 2Fe^{2+} \quad (31)$$

$$UO_3 + 2H^+ \rightarrow UO_2^{2+} + H_2O \quad (32)$$

$$UO_2^{2+} + SO_4^{2-} \rightleftharpoons UO_2SO_4 \quad (33)$$

$$UO_2SO_4 + SO_4^{2-} \rightleftharpoons UO_2(SO_4)_2^{2-} \quad (34)$$

$$UO_2(SO_4)_2^{2-} + SO_4^{2-} \rightleftharpoons [UO_2(SO_4)_3]^{4-} \quad (35)$$

(iii) Ion exchange

In the ion exchange process[7] the leach liquor is passed through a bed of anion exchange resin beads which are loaded with chloride or in some cases nitrate. The resin will normally be a polymer carrying quaternary amine functions and having the generalized formula $Pol(NR_3)_x{}^+Cl_x{}^-$, where Pol represents a polymer chain such as styrene–divinylbenzene copolymer, R = alkyl and x is an indeterminate large number. Total loading of the resin with $UO_2(SO_4)_2^{2-}$ would then be represented by equation (36). Impurities in the leach liquor may compete for resin sites and reduce the efficiency of uranium uptake as well as adding impurities to the desorbed product solution. Metals which do not form anionic complexes under the relevant conditions will not bind to the resin. However, molybdate and vandate, for example, are strongly bound and compete with the uranyl species for binding sites. Normally vanadium is present as V^{IV} which is not bound, but if any V^V is present in the leach liquor it must be reduced to V^{IV}. Iron in the form of Fe^{III} also forms sulfate complexes which bind to anion exchange resins, though not as strongly as the uranyl complex. Iron phosphate and polythionate complexes present a more severe problem since their binding to the resin is not completely reversible. Thus after a number of adsorption–desorption cycles the capacity of the resin can be significantly reduced by such species. Although it does not bind to cationic resin sites, silica can also impair resin performance by forming a polymeric deposit which restricts the diffusion of ions in and out of resin binding sites. While it is not an impurity in the system, HSO_4^- is more strongly bound than the uranyl species and can reduce the resin capacity. To avoid this it is desirable to operate the column at high pH to move the equilibrium shown in equation (37) to the left, thus producing SO_4^{2-} which is not strongly bound.

$$Pol(NR_3)_xCl_x + \tfrac{x}{2}UO_2(SO_4)_2^{2-} \rightleftharpoons Pol(NR_3)_x[UO_2(SO_4)_2]_{x/2} + xCl^- \quad (36)$$

$$H^+ + SO_4^{2-} \rightleftharpoons HSO_4^- \quad (37)$$

Unfortunately pH values above *ca.* 2 are not acceptable since the precipitation of uranyl complexes can occur under such conditions. Careful control of the process conditions is thus necessary for optimum performance to be achieved. Desorption of the purified uranyl product is effected using chloride or nitrate eluant solutions. A 1 M sodium chloride solution containing 0.05 M H_2SO_4 might typically be used with the Cl^- displacing $UO_2(SO_4)_3^{4-}$ from the resin and the H_2SO_4 lowering the pH to prevent the precipitation of uranyl complexes. Elution with 1 M nitrate solutions containing 0.1–0.4 M free acidity is more efficient and is often followed by treatment

with lime to give a pH of 3.5 and to remove iron and phosphate. The final product from this process is obtained by the addition of sodium or ammonium hydroxide to precipitate the product yellowcake. The major species in solution during the hydrolysis of uranyl salts of various strong acids were found[86,87] to be the dinuclear and trinuclear complexes $(UO_2)_2(OH)_2^{2+}$ and $(UO_2)_3(OH)_5^+$, as found in carbonate media.[73] However, the precipitation reaction is complex and, in proportions depending on the conditions, a variety of simple hydroxy and basic sulfate species may be formed along with the diuranate.[88]

The oxidative leaching of uraniferous ores can also be achieved by autotrophic bacteria, which obtain energy from the oxidation of Fe^{II}, sulfur or sulfide.[89] *Thiobacillus ferrooxidans*, *Thiobacillus thiooxidans* and *Ferrobacillus ferrooxidans* are the major species responsible for leaching of this type and, in the presence of oxygen, they convert sulfides to sulfate and Fe^{II} to Fe^{III}, thus providing both acid and oxidant for leaching. In one example, mine drainage water from the Stanrock mine in Canada had a pH of 2.4 and a uranium content of 0.13 g dm^{-3} as U_3O_8. In the 1960s the total uranium output of the mine was derived from ion exchange treatment of this bacterially acidified mine water.

(iv) Solvent extraction

An alternative to the ion exchange process described above is provided by solvent extraction. Unlike ion exchange, which is a batch process, solvent extraction can operate continuously in counter current contactors such as the mixer settlers or pulsed columns described in Section 65.2.4.2. This gives rise to lower operating costs for uranium purification processes which utilize solvent extraction. The principles of solvent extraction are considered in more detail in Section 65.2.4.2 and a detailed account of the solution chemistry of the actinides as it relates to solvent extraction processes has been given by Rydberg and coworkers.[90] There are three main types of reagent, namely cationic, anionic or neutral, which may be used to extract uranium from pregnant leach liquors. The first of these is used in a process which has considerable chemical similarity to the use of ion exchange resins and is sometimes referred to as a liquid anion exchange process. It involves contacting the acidic aqueous leach liquor with an organic phase containing an alkylamine extractant dissolved in a hydrocarbon diluent, usually kerosene. Tertiary amine reagents, such as triisooctylamine, are more selective for uranyl species than primary amines, but will not extract carbonate complexes of UO_2^{2+} formed under alkaline conditions. Such complexes can be extracted using quaternary amines, but it can be difficult to define suitable diluents for these extractants. Alamine 336 is the commercial tertiary amine reagent most widely used for uranium extraction and contains a mixture of C_8H_{18}, C_9H_{20} or $C_{10}H_{22}$, with $R = C_8H_{18}$ predominating as the alkyl substituents. Molybdate and vanadate are also well extracted by alkylamines and may not be readily separated from uranium in this process. The extracted uranyl complexes are stabilized in the organic phase by ion pair and micelle formation.[91] This can lead to anomalous extraction in which the metal distribution coefficient exhibits kinetic control and becomes highly dependent on mixing intensity within the contactor. As with resins, any HSO_4^- present may compete for the extractant so that low pH values can lead to decreased uranium extraction. A substantial body of data on the extraction of UO_2^{2+} from sulfuric acid by alkylamines is available.[92-97] The distribution coefficient $D_{U^{VI}}$, defined in equation (38), reaches a maximum at about 0.05 M H_2SO_4. However, by using 5% trioctylamine (TOA) in xylene, effectively quantitative uranium extraction is possible for solutions containing between 0.005 and 0.25 M H_2SO_4. Only above 0.5 M H_2SO_4 does $D_{U^{VI}}$ fall below 100. The variation of $D_{U^{VI}}$ with acid concentration for different organic phase concentrations of trioctylamine (TOA) in benzene is shown[93] in Figure 11. Similar results were obtained using tridodecylamine (TDA) but in this case the maximum value of $D_{U^{VI}}$ between 0.01 and 0.5 M H_2SO_4 was indeterminate and greater than 300.[94] The magnitude of $D_{U^{VI}}$ was found to vary in an almost linear fashion with temperature over the range 10-50 °C. In the case of 0.1 M TDA in benzene, $D_{U^{VI}}$ fell from 8 for 1.0 M H_2SO_4 and 6 for 0.02 M H_2SO_4 at 10 °C to about 4 in both cases at 50 °C. Broadly similar results were obtained for TOA with $D_{U^{VI}}$ falling from *ca.* 5 to *ca.* 3 under the same conditions.

$$D_{U^{VI}} = \frac{\text{Total } U^{VI} \text{ concentration in the organic phase}}{\text{Total } U^{VI} \text{ concentration in the aqueous phase}} \tag{38}$$

The nature of the uranyl species involved in the extraction process has been investigated. A general reaction according to equation (39) was proposed by Allen,[95] while Sato proposed[96] specific reactions according to equations (40) and (41) for uranyl extraction from 0.02 and

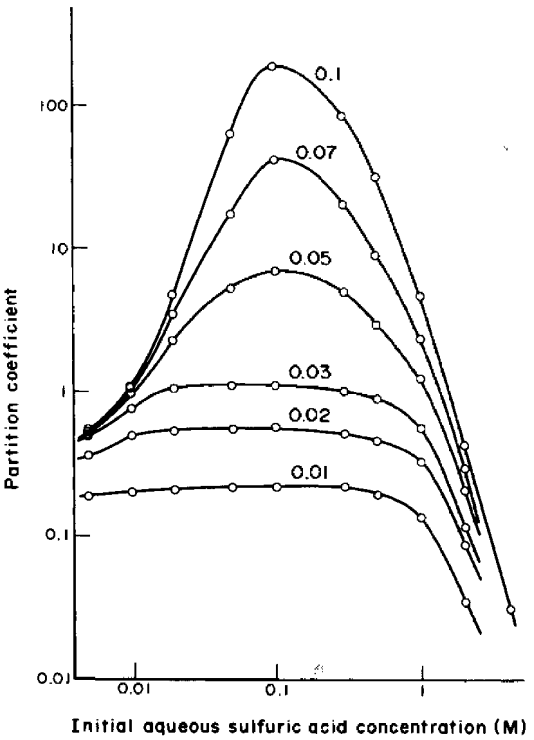


Figure 11 The extraction of U^{VI} from sulfuric acid solution by TOA in benzene.[93] Curves are labelled by TOA concentration (M)

1.0 M H_2SO_4 respectively into TOA or TDA with benzene as the diluent. (The subscripts (aq) and (org) refer to the aqueous and organic phases respectively and R = *n*-C_8H_{18} or *n*-$C_{10}H_{22}$). The heats of reaction for these processes are summarized in Table 8. Better extraction efficiencies were obtained using alkylcyclohexylamines although branched alkyl chains gave poorer efficiencies than linear chains.[96] In the case of these secondary amines the extraction process was found to be described by equations (42) and (43) for the 0.02 M H_2SO_4 and 1.0 M H_2SO_4–benzene systems respectively. The extraction enthalpies are again given in Table 8. Differential thermal analysis and thermogravimetric analysis of the material obtained by evaporation of the solvent phase of the UO_2^{2+}–H_2SO_4/TDA–benzene system confirmed that $(C_{12}H_{25})_3NH_4UO_2(SO_4)_3(OH_2)_3$ was the composition of the extracted species, similar conclusions being reached in the case of TOA also.[97]

$$nx(R_3NH)HSO_{4(org)} + \frac{n}{2}(1-x)(R_3NH)_2SO_{4(org)} + UO_2SO_{4(aq)} \rightleftharpoons (R_3NH)_nUO_2(SO_4)_{(n/2+1)(org)} + \frac{n}{2}xH_2SO_{4(aq)} \quad (39)$$

$$UO_2SO_{4(aq)} + 2(R_3NH)_2SO_{4(org)} \rightleftharpoons (R_3NH)_4[UO_2(SO_4)_3]_{(org)} \quad (40)$$

$$UO_2SO_{4(aq)} + 4(R_3NH)HSO_{4(org)} \rightleftharpoons (R_3NH)_4[UO_2(SO_4)_3]_{(org)} + 2H_2SO_{4(aq)} \quad (41)$$

$$UO_2SO_{4(aq)} + 2(RR'NH_2)_2SO_{4(org)} \rightleftharpoons \{(RR'NH_2)_2SO_4\}_2UO_2SO_{4(org)} \quad (42)$$

$$UO_2SO_{4(aq)} + 4(RR'NH_2)HSO_{4(org)} \rightleftharpoons \{(RR'NH_2)_2SO_4\}_2UO_2SO_{4(org)} + 2H_2SO_{4(aq)} \quad (43)$$

$$UO_2(NO_3)^{n-}_{(2+n)(aq)} + nR_3NHNO_{3(org)} \rightleftharpoons (R_3NH)_nUO_2(NO_3)_{(2+n)(org)} + nNO_3^-{}_{(aq)} \quad (44)$$

The extraction of UO_2^{2+} by tertiary amines in the nitric acid–xylene system has also been investigated and in this case the reaction was described by equation (44) where *n* ranged from 1.0 to 1.7 depending upon the uranium, acid and nitrate concentrations.[98] The low equilibrium constant (0.32) for the formation of $[UO_2(NO_3)_3]^-$ from $UO_2(NO_3)_2$ leads to small partition coefficients, $D_{U^{VI}}$, at low acid concentrations. However, above 6 M HNO_3 inextractable $HUO_2(NO_3)_3$ becomes the dominant species in the aqueous phase. Consequently the value of $D_{U^{VI}}$ between nitric acid and 10% trilaurylamine in xylene only reached a maximum of slightly

Table 8 Enthalpies of Extraction of Uranyl from Sulfuric Acid by Organoamines[82,83,85]

Extractant	*Enthalpy of extraction* (kJ mol^{-1}) 0.02 M H_2SO_4	1.0 M H_2SO_4
Tri-*n*-dodecylamine[82]	−7.32	−38.2
Tri-*n*-octylamine[83]	−8.61	−34.5
n-Dodecylcyclohexylamine[85]	−4.35	−21.7

over 1.0 between 5 and 7 M HNO_3. In order to obtain larger $D_{U^{VI}}$ values in such systems it is necessary to use high nitrate, and low acid, concentrations. These may be achieved by the addition of $NaNO_3$ or $Ca_2(NO_3)_2$ to the aqueous phase but this makes the use of tertiary amine reagents unattractive for the extraction of U^{VI} from nitric acid solutions. These results are in marked contrast to the large $D_{U^{VI}}$ values attainable when using tertiary amines to extract UO_2^{2+} from sulfuric acid solutions.

In operating solvent extraction systems the presence of $(R_3NH)HSO_4$ and $(R_3NH)_2SO_4$ can lead to the formation of a third phase rich in these materials, and of low solubility in the aqueous or organic phases. In order to prevent this it is necessary to add a modifier to increase their solubility in the diluent. The modifier is usually a long-chain primary alcohol which also assists phase disengagement after mixing. A typical extraction system might thus contain 5% by weight, or 0.1 M, tertiary amine and about 3% of an alcohol, such as 2-ethylhexanol, dissolved in a hydrocarbon diluent such as kerosene or naphtha. The uranium may be back-extracted from the loaded organic phase by contact with chloride or nitrate solutions according to equation (45) in a similar manner to that employed with resins. Alternatively, carbonate solutions may be used according to equation (46). In some cases, direct conversion to diuranate may be effected by contact with solutions of NaOH, or NH_4OH solutions or by using MgO slurry as shown in equation (47).[51]

$$(R_3NH)_2UO_2(SO_4)_{2(org)} + 2NO_3^-{}_{(aq)} \rightarrow 2(R_3NH)NO_{3(org)} + UO_2^{2+}{}_{(aq)} + 2SO_4^{2-}{}_{(aq)} \quad (45)$$

$$(R_3NH)_2UO_2(SO_4)_{2(org)} + 4Na_2CO_{3(aq)} \rightarrow 2R_3N_{(org)} + Na_4UO_2(CO_3)_{3(aq)} + 2Na_2SO_{4(aq)} + H_2O_{(aq)} + CO_2 \quad (46)$$

$$2(R_3NH)_2UO_2(SO_4)_{2(org)} + 5MgO_{(aq)} \rightarrow 4R_3N_{(org)} + MgU_2O_7 + 4MgSO_{4(aq)} + 2H_2O_{(aq)} \quad (47)$$

A novel variation of the amine extraction process is exemplified by the use of coupled transport in the extraction of UO_2^{2+} through a solid supported liquid membrane.[99] Hollow fibres of Celgard 2400, a polysulfane, were impregnated with a 30% solution of Alamine 336 in an aromatic solvent. These were assembled into bundles to make up modules through which the feed solution was cycled against a product solution of a high pH in a continuous countercurrent pilot plant. The chemical aspects of the membrane transport process are shown in Figure 12. Using a model feed containing UO_2^{2+} (2000 p.p.m.), VO_3^- (100 p.p.m.), MoO_4^{2-} (100 p.p.m.) and $(Fe^{2+} + Fe^{3+})$ (1140 p.p.m.) in sulfuric acid at pH 1, a product stream containing UO_2^{2+} (30 000 p.p.m.), VO_3^-

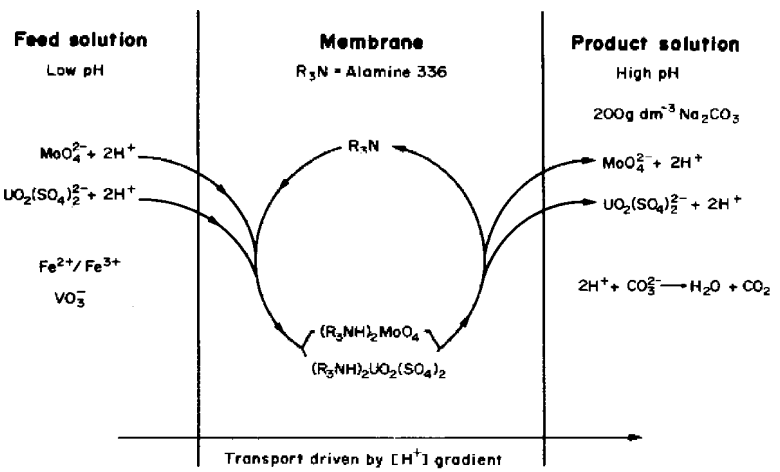


Figure 12 A coupled transport mechanism[99] for the membrane extraction of U^{VI}

(<0.1 p.p.m.), MoO_4^{2-} (1500 p.p.m.) and ($Fe^{2+}+Fe^{3+}$) (<0.1 p.p.m.) was obtained. Uranium concentrations as low as 3–4 p.p.m. in the raffinate could be achieved giving a concentration ratio approaching 10^4 between the two streams. The uranium could be selectively precipitated using peroxide[100] according to equation (48) to leave a supernatant enriched in molybdenum but depleted in iron and vanadium.

$$UO_2^{2+}+H_2O_2+2H_2O \rightarrow UO_4\cdot 2H_2O+2H^+ \quad (48)$$

The second type of reagent which may be used for uranium(VI) extraction is potentially anionic and is used in a process which has been referred to as liquid cation exchange. Unlike the situation with amine reagents, where the extractant cation does not form an inner sphere complex with UO_2^{2+}, these reagents form complexes by binding directly to the metal. Thus they do not rely on the formation of suitable anionic species such as $[UO_2(SO_4)_3]^{4-}$ or $[UO_2(NO_3)_3]^-$ and are effective in removing UO_2^{2+} from solutions in which such complexes are not major components. The reagents of this type, which are most widely used for bulk uranium extraction, are the mono- and di-alkyl phosphates, and in particular di-2-ethylhexyl phosphoric acid, $(C_8H_{17}O)_2P(O)OH$, (HDEHP).[4] Such reagents are usually used with an added modifier such as tributyl phosphate, $(Bu^nO)_3PO$(TBP), which is present to prevent the formation of a third phase containing sodium dialkyl phosphates during the back extraction stage, and to assist phase disengagement after mixing. Such additives may also exhibit a synergistic effect on UO_2^{2+} extraction. This results from adduct formation which increases the partition coefficient, $D_{U^{VI}}$, as described later in this section. A typical extractant formulation might thus contain 3–5% each of TBP and HDEHP in a hydrocarbon diluent such as kerosene. Alternatively a 0.1 M solution of monododecyl phosphoric acid (DDPA) may be used without any added synergist. Outline flow diagrams for the DAPEX process,[101] which utilizes TBP/HDEHP mixtures, the DDPA process and the AMEX process, which utilizes a tertiary amine extractant, are shown in Figure 13 for comparison.

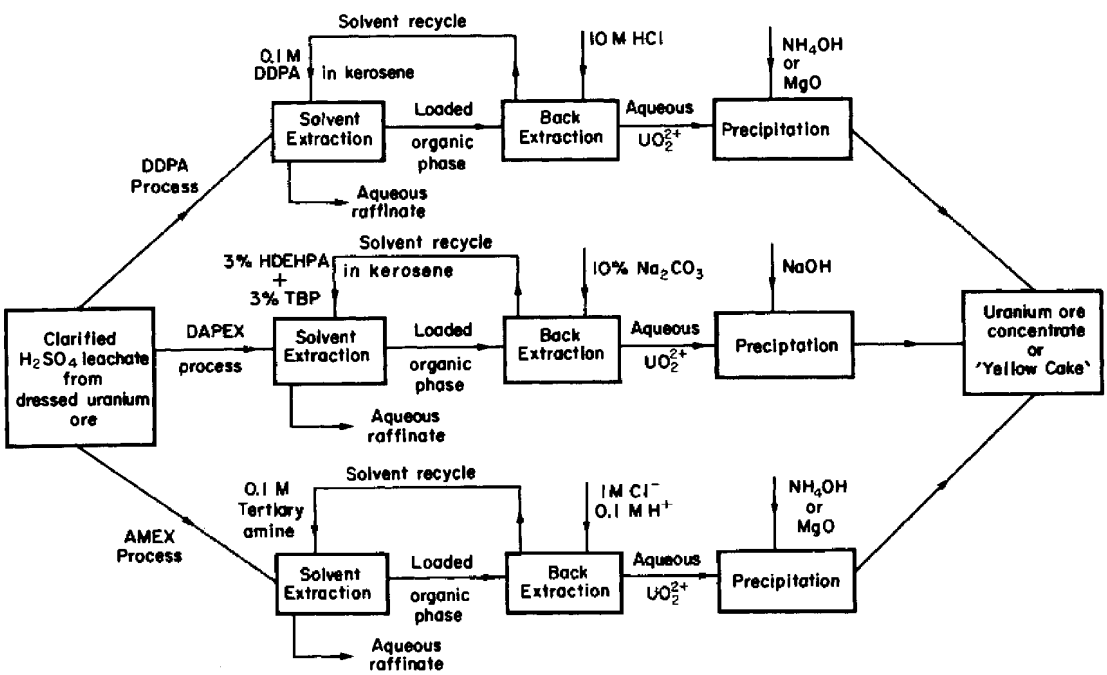
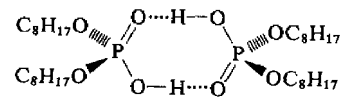


Figure 13 Outline flowsheets for uranium purification using the DPPA, DAPEX or AMEX processes[51]

The chemistry of UO_2^{2+} extraction by organophosphate anions is complicated by solvent association reactions. Thus while HDEHP is monomeric in polar diluents of high dielectric constant, such as methanol, it is dimeric in nonpolar solvents such as benzene or *n*-hexane.[102] In the case of mono-2-ethylhexyl phosphoric acid (H_2MEHP), association was found to occur to an even greater extent and isopiestic measurements indicated an average of 6.2 molecules were associated in benzene, rising to 14.5 in *n*-hexane. On the basis of the known solid state structure[103] of the dimer of $(PhCH_2O)_2P(O)OH$, (1) was presumed to represent the solution structure of $(HDEHP)_2$.



(1)

Dibutyl phosphoric acid (HDBP) also dimerizes in nonpolar solvents and solutions of HDBP in kerosene contacting aqueous nitric acid equilibrate to produce $(HDBP)_2$, $HDBP{\cdot}H_2O$ and $HDBP{\cdot}HNO_3$ in both phases. In addition, the organic phase contains $(HDBP)_2{\cdot}H_2O$ and the aqueous phase $(Bu^nO)_2PO_2^-$ (DBP^-) in equilibrium with HDBP.[104] Such equilibria complicate the stoichiometry of U^{VI} extraction from aqueous sulfuric acid solutions. Thus the extraction of UO_2^{2+} from aqueous perchloric acid was described[105] by equation (49) but in the case of sulfuric acid this reaction was only found to apply for acid concentrations above 0.15 M.[106] At lower acidities of 0.15 M and below the extraction reaction was described by equation (50), the net result of which was to give the extraction stochiometry shown in equation (51) for conditions of

$$UO_2^{2+}{}_{(aq)} + 2(HDEHP)_{2(org)} \rightleftharpoons [UO_2\{H_2(DEHP)_4\}]_{(org)} + 2H^+{}_{(aq)} \quad (49)$$

$$UO_2\{H_2(DEHP)_4\}_{(org)} + UO_2^{2+}{}_{(aq)} + (HDEHP)_{2(org)} \rightleftharpoons (UO_2)_2\{H_2(DEHP)_6\}_{(org)} + 2H^+{}_{(aq)} \quad (50)$$

$$2UO_2^{2+}{}_{(aq)} + 3(HDEHP)_{2(org)} \rightleftharpoons (UO_2)_2\{H_2(DEHP)_6\}_{(org)} + 4H^+{}_{(aq)} \quad (51)$$

low acidity. Some data for U^{VI} extraction from sulfuric acid by varying HDEHP concentrations in kerosene are presented in Figure 14. The variation of the partition coefficient $D_{U^{VI}}$ with aqueous

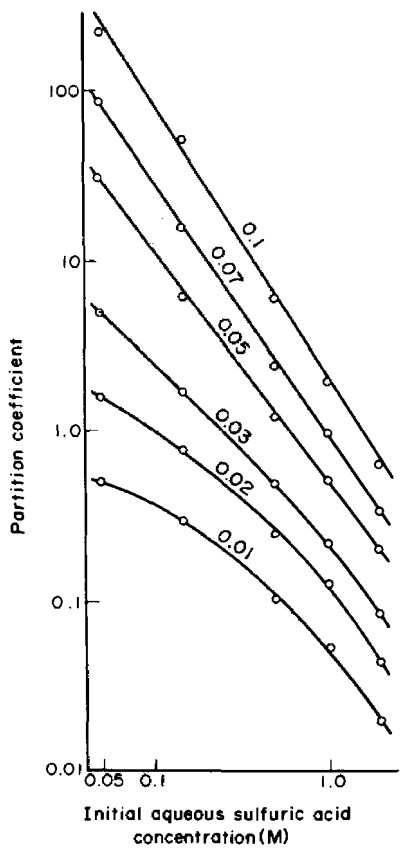


Figure 14 The extraction of U^{VI} from H_2SO_4 by HDEHP in kerosene.[106] Curves are labelled by HDEHP concentration (M)

sulfuric acid and uranyl sulfate concentrations is also shown in Figure 15 for 0.1 M HDEHP in kerosene. The value of $D_{U^{VI}}$ decreased on heating from 10 to 50 °C and the heats of reaction for the extraction processes were found to be −7.15 and −10.1 kJ mol^{-1} respectively for solutions containing 4.5 g dm^{-3} uranyl sulfate in 0.15 M and 1.0 M H_2SO_4.

The structure of the species $[UO_2\{H_2(DEHP)_4\}]$ has been the subject of some speculation and the coordination arrangement shown in (2) with R = 2-ethylhexyl was proposed.[107] However, this

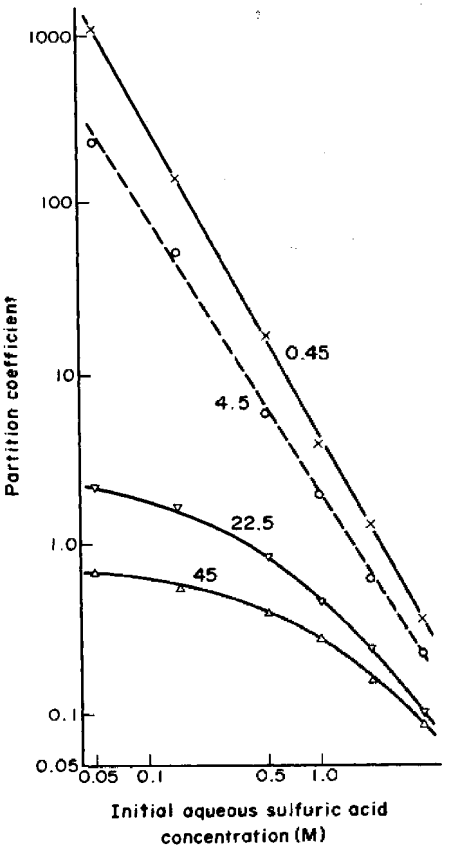
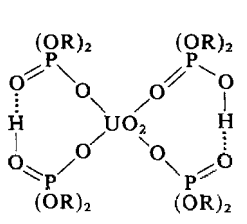
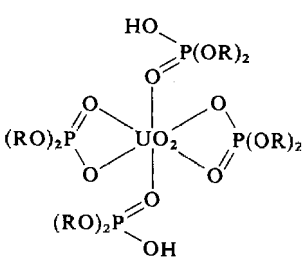


Figure 15 The effect of uranium concentration on uranium extraction from H_2SO_4 by 0.1 M HDEHP in kerosene.[106] The curves are labelled with U concentration (g dm^{-3})

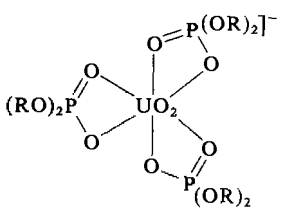
contains a six-coordinate metal centre and eight-membered chelate rings, both of which are structural features unlikely to be favoured by U^{VI}. In view of the tendency of uranyl species to form adducts with phosphine oxides or TBP, formula (**3**) would seem to offer a realistic alternative structure. Unfortunately this type of structure is not in accord with IR data for $[UO_2\{H_2(DBP)_4\}]$ in carbon tetrachloride solution.[108] Consequently structure (**4**) was proposed but no evidence as to the location of the additional proton and HDEHP molecule was found. The structure which is adopted may be influenced by steric factors and it has been found that branching in the alkyl chain of a dialkyl phosphate extractant can reduce the partition coefficient for UO_2^{2+}.[107] Unfortunately, reagents containing long straight-chain alkyl groups may form stable emulsions which are difficult to break. Some branching of the alkyl chain as in HEHDP may thus be desirable for operational reasons. Steric effects have also been found in the extraction of UO_2^{2+} by phosphinic acid derivatives. However, conflicting results were obtained in that for one system the less sterically hindered reagent with the more basic phosphonyl group was the poorer extractant.[109] In the other system studied it was the least sterically hindered and most acidic reagent which was the better extractant.[110] There is apparently an interplay between steric factors and the donor properties of the extractant which does not allow simple generalizations to be made.



(**2**)



(**3**)



·H^+·HDEHP

(**4**)

In polar diluents containing monomeric HDEHP the extraction of UO_2^{2+} may be described by equation (52). However, although this stoichiometry was found to apply to the extraction of UO_2^{2+} from aqueous HNO_3 and HCl into *n*-pentanol solutions containing less than 0.1 M HDEHP, at HDEHP concentrations above. 0.1 M equation (49) applied.[111] The extraction of UO_2^{2+} from nitric acid into HDEHP solutions in kerosene has also been studied and was not found to follow equation (49).[112] At acid concentrations of less than 2 M, equation (51) described the extraction reaction while at higher acidities nitrate complexation was also involved, as shown in equation (53). The variation of $D_{U^{VI}}$ with nitric acid concentration is shown in Figure 16. It was found that HNO_3 is also extracted into the organic phase of these systems according to equation (54) and that changes in organic phase acidity with uranium concentration were consistent with the ion exchange mechanism at lower acidities. The effect of increasing the temperature from 10 to 50 °C was to reduce the value of $D_{U^{VI}}$ and the enthalpy of UO_2^{2+} extraction from 6 M HNO_3 according to equation (53) was estimated at -19.7 kJ mol^{-1}, compared with -10.3 kJ mol^{-1} for 0.5 M HNO_3.

$$UO_2^{+}{}_{(aq)} + 2HDEHP_{(org)} \rightleftharpoons UO_2(DEHP)_{2(org)} + 2H^{+}{}_{(aq)} \quad (52)$$

$$UO_2^{2+}{}_{(aq)} + 2NO_3^{-}{}_{(aq)} + (HDEHP)_{2(org)} \rightleftharpoons [UO_2(NO_3)_2(HDEHP)_2]_{(org)} \quad (53)$$

$$HNO_{3(aq)} + (HDEHP)_{2(org)} \rightleftharpoons (HDEHP)_2 \cdot HNO_{3(org)} \quad (54)$$

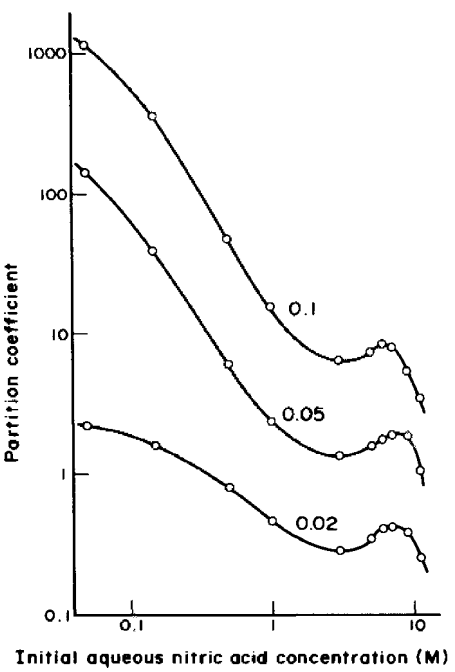


Figure 16 The extraction of uranyl nitrate (5 g dm^{-3}) from nitric acid by HDEHP in kerosene at 20 °C.[112] Curves are labelled with HDEHP concentration (M)

The extraction of UO_2^{2+} from chloride media using other isomers of $(C_8H_{17}O)_2P(O)OH$ has been studied. Both di-*n*-octyl phosphoric acid (HDOP)[113] and dineooctyl phosphoric acid[114] as 0.027 M solutions in benzene or heptane gave rise to extraction stoichiometries of the type shown in equation (50). They also exhibited larger $D_{U^{VI}}$ values than HDEHP. Similar extraction chemistry was also observed for the phosphinic acid derivatives RPhP(O)OH, where R = octyl or cyclooctyl, and the same equation applied.[115] A direct comparison of HDEHP and its phosphonate analogue $(C_8H_{17}O)(C_8H_{77})P(O)OH$ (HEHEHP) has also been made using these reagents as 0.027 M solutions in toluene to extract UO_2^{2+} from chloride, perchlorate or nitrate media.[116] Both reagents again showed analogous extraction stoichiometries of the type given in equation (49) but the phosphonate, HEHEHP, gave rise to values of $D_{U^{VI}}$ almost twice those obtained with HDEHP.

The extraction of UO_2^{2+} from nitric acid solutions by the shorter alkyl chain organophosphate HDBP has been investigated in various diluents by Hardy.[117] The variation of $D_{U^{VI}}$ with nitric acid concentration for UO_2^{2+} extraction into 0.01 M and 0.05 M HDBP in toluene is shown in

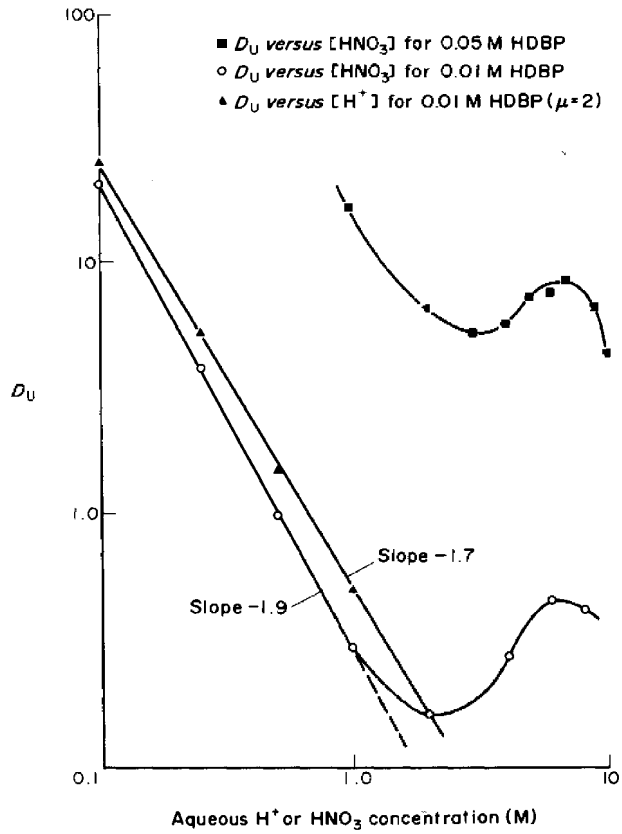


Figure 17 The variation of D_U with $[H^+]$ and $(HNO_3]$ for 0.01 M and 0.05 M HDBP in toluene[117]

Figure 17. An empirical model was developed to describe the extraction process, taking account of the observation that $[UO_2(DBP)_2(HDBP)_2]$ was the predominant uranyl species in the organic phase at aqueous phase acidities of less than 2 M, while $[UO_2(NO_3)_2(HDBP)_2]$ predominated at higher acidities. The curves derived from this model, and a revised model which took into account the presence of other organic phase species such as $H[UO_2(NO_3)_3]\cdot(HDBP)$, are shown in Figure 18. The latter model gave a good description of the system in the aqueous phase acidity range 1–7 M.

The partition coefficient for UO_2^{2+} extraction by dialkyl phosphoric acid reagents may be increased by the addition of a neutral ligand such as TBP. In such cases the added ligand is said to act as a synergist and the effect of various synergists on $D_{U^{VI}}$ for the extraction of UO_2^{2+} from 1.5 M H_2SO_4 by HDEHP is illustrated in Figure 19.[90,118] These results show tributylphosphine oxide (TBPO) to be a more powerful synergist than its less basic phosphate analogue, TBP. In the organic phase the association reactions[119] shown in equations (55) and (56) lead to a decrease in the free HDEHP concentration for high concentrations of synergist, S. Thus the curves in Figure 19 exhibit maxima with $D_{U^{VI}}$ decreasing at higher synergist concentrations. The synergistic effect was proposed by Baes[120] to arise from the formation of an adduct according to equation (57) rather than by substitution reactions such as those shown in equations (58) and (59). These had been proposed in studies[121] of UO_2^{2+} extraction from 0.1 M H_2SO_4 into carbon tetrachloride solutions of HDBP which had identified the substitution products $[UO_2\{H(DBP)_3\}\cdot TBP]$ for S = TBP and $[UO_2\{H(DBP)_3\}\cdot TOPO]$ and $[UO_2(DBP)_2\cdot(TOPO)_2]$ for S = trioctylphosphine oxide (TOPO). The species $[UO_2\{H(DEHP)_3\}\cdot TOPO]$ was also proposed by Zangen[122] and equilibrium constants were reported[123] for $[UO_2\{H_2(DBP)_4\}\cdot S]$, $[UO_2\{H(DBP)_3\}\cdot S]$, $[UO_2(DBP)_2\cdot S]$, $[UO_2(DBP)_2\cdot S_2]$, $UO_2(SO_4)\cdot S$ and $UO_2(SO_4)\cdot S_2$, where S = TBP or TOPO, indicating that substitution reactions did contribute to the mechanism of synergism. Amines such as tri-*n*-octylamine (TOA) may also act as synergists in the dialkyl phosphoric acid extraction of U^{VI}, as shown[124] for the UO_2^{2+}–H_2SO_4–H_2O/HDBP–TOA–benzene system in which the extracted species was thought to be $TOAH[UO_2(SO_4)\{H(DBP)_2\}]$. Similar results were obtained using HDEHP in place of HDBP. When the mole ratio of TOAH·DBP to uranium fell below three, two polymeric species of formula $[UO_2(SO_4)(DBP)]_n^{n-}$ were thought to be extracted as their $TOAH^+$ salts. These results were surprising since it was expected that the amine would exert an antagonistic effect. That is,

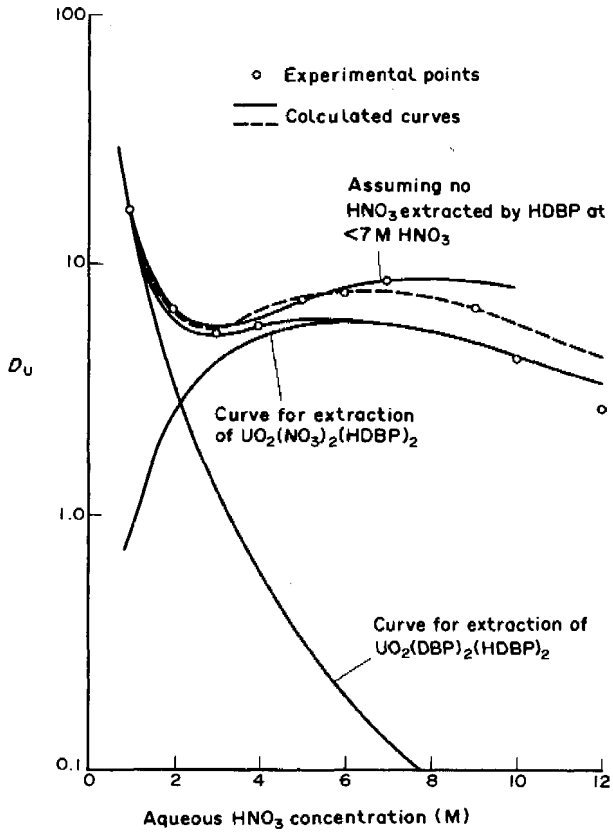


Figure 18 Calculated and experimental D_U values for the 0.05 M HDBP in toluene/HNO_3 system[117]

it would suppress UO_2^{2+} extraction by competing for the organic phase HDBP through the formation of stable adducts in a similar manner to HDEHP, which forms TOAH·DEHP in the organic phase.[125] While this appeared to be the case at low H_2SO_4 concentrations, for 1.0 M and 2.0 M H_2SO_4 the formation of the amine sulfate broke down the TOA·HDBP adducts, decreasing the antagonistic effect. The higher organic phase solubility of the mixed sulfate-DBP^- complex of UO_2^{2+} compared with its homoleptic sulfate analogue could then lead to synergism in the

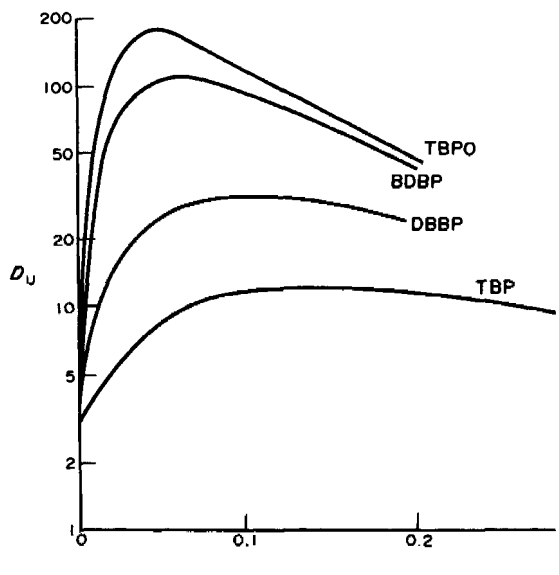


Figure 19 Examples[90] of the synergistic extraction of U^{VI} by 0.1 M HDEHP in kerosene with various neutral ligands B from an aqueous phase containing 1.5 M H_2SO_4 and 0.04 M U^{VI}

extraction process. Viewed in these terms it may be better to describe this process as synergic enhancement of the tertiary amine extraction of UO_2^{2+} by the addition of HDBP.

$$(HDEHP)_{2(org)} + S_{(org)} \rightleftharpoons (HDEHP)_2S_{(org)} \quad (55)$$

$$\tfrac{1}{2}(HDEHP)_{2(org)} + S_{(org)} \rightleftharpoons HDEHP{\cdot}S_{(org)} \quad (56)$$

$$UO_2\{H_2(DEHP)_4\}_{(org)} + S_{(org)} \rightleftharpoons UO_2\{H_2(DEHP)_4\}{\cdot}S_{(org)} \quad (57)$$

$$UO_2\{H_2(DEHP)_4\}_{(org)} + (HDEHP)_2S_{(org)} \rightleftharpoons UO_2\{H_2(DEHP)_4\}{\cdot}S_{(org)} + (HDEHP)_{2(org)} \quad (58)$$

$$UO_2\{H_2(DEHP)_4\}_{(org)} + (HDEHP)_2S_{(org)} \rightleftharpoons [UO_2\{H(DEHP)_3\}{\cdot}S]_{(org)} + (HDEHP)_{2(org)} \quad (59)$$

Uranium extracted by HDEHP may be returned to the aqueous phase by contact with a strong acid, which reverses the extraction reaction. Alternatively, contact with sodium carbonate solution may be used to strip the UO_2^{2+} from the organic phase as carbonate complexes. This approach is used in the DAPEX process and reactions such as that given by equation (60) may be proposed to represent the transfer process.

$$UO_2\{H_2(DEHP)_4\}_{(org)} + 3CO_3^{2-}{}_{(aq)} + 2H_2O_{(aq)} \rightleftharpoons [UO_2(CO_3)_3]^{4-}{}_{(aq)} + 2OH^-{}_{(aq)} + 2(HDEHP)_{(org)} \quad (60)$$

$$[UO_2(H_2O)_6]^{2+}{}_{(aq)} + 2(H_2DDP)_n{\cdot}xH_2O_{(org)} \rightleftharpoons [UO_2(HDDP)_2{\cdot}2(H_2DDP)_{(n-1)}{\cdot}yH_2O]_{(org)} + 2H^+{}_{(aq)} + (x+6-y)H_2O_{(aq)} \quad (61)$$

$$[UO_2(H_2O)_6]^{2+}{}_{(aq)} + 2(H_2MBP)_{n(org)} \rightleftharpoons [UO_2(HMBP)_2{\cdot}2(H_2MBP)_{(n-1)}{\cdot}2H_2O]_{(org)} + 2H^+{}_{(aq)} + 4H_2O_{(aq)} \quad (62)$$

$$[UO_2(HDDP)_2{\cdot}2(H_2DDP)_{(n-1)}{\cdot}yH_2O]_{(org)} + (n-1)[UO_2(H_2O)_6]^{2+}{}_{(aq)} \rightleftharpoons n[UO_2(HDDP)_2{\cdot}zH_2O]_{(org)} + (2n-2)H^+{}_{(aq)} + \{(y-6)+n(6-z)\}H_2O_{(aq)} \quad (63)$$

$$[UO_2(HMBP)_2{\cdot}2(H_2MBP)_{(n-1)}2H_2O]_{(org)} + (n-1)[UO_2(H_2O)_6]^{2+}{}_{(aq)} \rightleftharpoons n[UO_2(HMBP)_2{\cdot}2H_2O]_{(org)} + (2n-2)H^+{}_{(aq)} + (4n-4)H_2O_{(aq)} \quad (64)$$

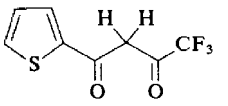
The mechanism of UO_2^{2+} extraction by monoalkyl phosphoric acid reagents appears to be a more complex process than for their dialkyl counterparts. This results from the polymerization of the monoalkyl phosphate in the organic phase and the hydration of the extracted uranyl species so that variable stoichiometries arise for the extractant/water/UO_2^{2+} complex. The extraction of UO_2^{2+} from sulfuric acid by mono-2,6,8-trimethylnonyl phosphoric acid (H_2DDP) and mono-*n*-butyl phosphoric acid (H_2MBP) as 0.05 M solutions in benzene was shown[126] to follow equations (61) and (62) when an excess of extractant was present. When an excess of uranium was present, equations (63) and (64) applied where *n*, *x*, *y* and *z* were variable numbers which depended upon the extent of extractant polymerization and hydration of the extracted species. Synergistic effects may also be found with the monoalkyl phosphoric acid extractants and in one recent example the use of tri-*n*-octylphosphine oxide (TOPO) as a synergist with H_2MEHP allowed the extraction of UO_2^{2+} from phosphoric acid solutions.[127] The uranium may be returned to the aqueous phase by contact with concentrated acid, which reverses the extraction process by protonation of the phosphate.

The association of uranium with vanadium in the mineral carnotite may give rise to significant quantities of vanadium in acid leach liquors. This too may be recovered by the HDEHP extraction process, either with the uranium or in a separate stage involving higher extractant concentrations. The vanadium was found to be extracted as V^{IV} species according to equation (65) at HDEHP concentrations less than 0.07 M and H_2SO_4 concentrations below 0.025 M.[128] At higher acidities of 0.05–0.4 M H_2SO_4 the reaction described by equation (66) becomes important. The vanadium partition coefficient, $D_{V^{IV}}$, decreased with the square of the hydrogen ion concentration but was not highly sensitive to sulfate concentration. Solutions of 0.2 M HDEHP in kerosene gave a $D_{V^{IV}}$ of 10 at 0.01 M H_2SO_4 falling to 0.01 at 0.7 M H_2SO_4. Iron is also present in the acid leachates and must be reduced to inextractable Fe^{II} since Fe^{III} is extracted by HDEHP to an extent which impairs uranium purification.

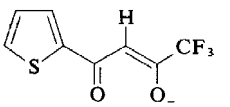
$$2VO^{2+}{}_{(aq)} + 3(HDEHP)_{2(org)} \rightleftharpoons (VO)_2\{H_2(DEHP)_6\}_{(org)} + 4H^+{}_{(aq)} \quad (65)$$

$$VO^{2+}{}_{(aq)} + 2(HDEHP)_{2(org)} \rightleftharpoons (VO)\{H_2(DEHP)_4\}_{(org)} + 2H^+{}_{(aq)} \quad (66)$$

In addition to the organo-phosphate and -phosphinate reagents, a variety of other potentially anionic ligands has been proposed as extractants for UO_2^{2+}. Most notable among these are the



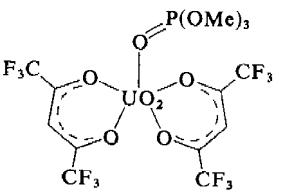
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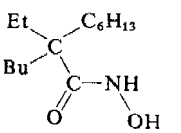
(6)

1,3-diketones[4] and in particular 1,1,1-trifluoro-4-(2-thenoyl)-butane-2,4-dione (HTTA) (**5**) has been widely studied.[92] This reagent can act as a monoanionic bidentate chelating agent in its enolate form (**6**). The related pentane-2,4-dione (Hacac) forms extractable species of formula $UO_2(acac)_2$ and $UO_2(acac)_2(Hacac)$ in solvent extraction systems.[129] Studies of the rate of reaction of UO_2^{2+} with 1,3-diketones have shown a higher rate constant for reaction with the diketo than with the keto-enol tautomer of Hacac.[130] Much more rapid reactions were found with HTTA and 1,1,1-trifluoro-pentane-2,4-dione, both of which reacted exclusively as their enol tautomers. Synergistic extraction in the presence of neutral donors such as TBP, TOPO or sulfoxides is well established for these reagents.[131] The formation of species having higher organic phase solubility through the displacement of water from the UO_2^{2+} coordination sphere is thought to be the basis for synergism, as shown in equation (67) for one example. Solvated species such as $[UO_2(TTA)_2 \cdot TBP]$ and $[UO_2(TTA)_2 \cdot 3TOPO]$ have been reported[132] and $[UO_2(DIK)_2 \cdot S]$ has been isolated where $DIK^- = TTA^-$ or $acac^-$ and S = TBP, $(PhCH_2)_2SO$ or Ph_2SO.[133] In these cases the stabilization of the synergetic complex was found to be entirely due to enthalpy, but where S = TOPO a significant entropy contribution to the stabilization was also found.[134] The solid-state structure of such an adduct containing 1,1,1,5,5,5-hexafluoropent-2-en-4-one-2-olate and trimethyl phosphate established the pentagonal bipyramidal coordination geometry (**7**).[135] Claims that the mixed ligand complex $[UO_2(NO_3)(TTA)(TBP)]$ was involved in the synergistic extraction of UO_2^{2+} from nitric acid have been refuted, $[UO_2(TTA)_2TBP]$ being identified as the extracted species.[136] The solvent extraction of UO_2^{2+} by hydroxamic acids[137] such as (**8**) and by thiophosphate esters has also been reported. Some thiophosphate derivatives were found to be better extractants for UO_2^{2+} than their oxygen analogues.[138]

$$[UO_2(TTA)_2(H_2O)]_{(org)} + TBP_{(org)} \rightleftharpoons [UO_2(TTA)_2TBP]_{(org)} + H_2O_{(aq)} \quad (67)$$



(7)



(8)

The third type of reagent which may be used for U^{VI} extraction is neutral in character. Methyl isobutyl ketone, $MeC(O)CH_2CMe_2$ (Hexone or MIBK), bis(2-butoxyethyl) ether, $(Bu^nOCH_2CH_2)_2O$ (Butex) and TBP are important examples of such reagents, amongst which TBP is now by far the most widely used by the nuclear industry. In addition to trialkyl phosphates, phosponates, $R(R'O)_2PO$, phosphinates, $R_2(R'O)PO$, and phosphine oxides, R_3PO, have been studied,[4,7,139] where R and R′ are usually alkyl. Recently, chelating neutral ligands such as $(Bu^nO)_2P(O)OCH_2CH_2XCH_2CH_2OP(O)(Bu^nO)_2$ (X = O or S) have been shown[140] to give higher $D_{U^{VI}}$ values than TBP for extractions from nitric acid, and the extraction of metals by phosphine oxide reagents containing chelating phosphoryl groups has been reviewed.[141] The mechanisms of metal ion extraction by neutral extractants have been classified either as heterogeneous metal ion dehydration occurring in the organic phase or as homogeneous with dehydration occurring in the aqueous phase.[90] The heterogeneous mechanism is the most commonly assumed, though often without foundation. This involves the prior formation of a neutral complex, which is then extracted at the phase boundary by displacement of water from the metal coordination sphere to form an organic phase complex in a combined chemical and mass transport process. Assuming a heterogeneous mechanism, the stages in this process may be illustrated by considering the extraction of UO_2^{2+} from chloride media by undiluted TBP.[142] The first stage is the formation of a neutral aqueous phase complex according to equation (68). This is followed by reaction with the extractant, which exists in the organic phase as $HCl \cdot (TBP)_2(H_2O)_6$ at HCl concentrations below 7 M, according to equation (69). At higher aqueous phase HCl concentrations the situation becomes complicated by competition between HCl and UO_2Cl_2 for the TBP. Further HCl is

extracted according to equation (70) and the new extractant species reacts with UO_2Cl_2 according to equation (71) giving an overall stoichiometry of 3TBP per UO_2^{2+} extracted as shown by equation (72). This system demonstrates some of the complications which can arise in TBP extraction when acid adducts and metal complexes of similar stability arise, as with $UO_2Cl_2(TBP)_2$ and $HCl{\cdot}TBP(H_2O)_3$. Also the nature of the extractant species in the organic phase may vary with extractant concentration and for diluted TBP a hydration number of four (not six) was found for the TBP·HCl adduct.[143] If the homogeneous mechanisms were operative, reactions such as those in equations (69) and (71) would occur wholly in the organic or the aqueous phase. In the latter case the $UO_2Cl_2(TBP)_2$ complex would then pass into the organic phase in a separate mass transfer step. Little information is available on which of these mechanistic possibilities applies in any particular UO_2^{2+} extraction system.

$$UO_2^{2+}{}_{(aq)} + 2Cl^-{}_{(aq)} \rightleftharpoons UO_2Cl_{2(aq)} \tag{68}$$

$$\{HCl(TBP)_2(H_2O)_6\}_{(org)} + UO_2Cl_{2(aq)} \rightleftharpoons UO_2Cl_2(TBP)_{2(org)} + HCl_{(aq)} + 6H_2O_{(aq)} \tag{69}$$

$$\{HCl(TBP)_2(H_2O)_6\}_{(org)} + HCl \rightleftharpoons 2\{HCl{\cdot}TBP(H_2O)_3\}_{(org)} \tag{70}$$

$$2\{HCl{\cdot}TBP(H_2O)_3\}_{(org)} + UO_2Cl_{2(aq)} \rightleftharpoons UO_2Cl_2(TBP)_{2(org)} + 2HCl_{(aq)} + 6H_2O_{(aq)} \tag{71}$$

$$\{HCl(TBP)_2(H_2O)_6\}_{(org)} + \{HCl{\cdot}TBP(H_2O)_3\}_{(org)} + UO_2Cl_{2(aq)} \rightleftharpoons UO_2Cl_2(TBP)_{2(org)} + \{HCl{\cdot}TBP(H_2O)_3\}_{(org)} + HCl_{(aq)} + 6H_2O_{(aq)} \tag{72}$$

TBP is not an effective reagent for the extraction of UO_2^{2+} from sulfuric acid solutions. The value of $D_{U^{VI}}$ for 30% TBP in benzene ranges from 0.05 at 0.5 M H_2SO_4 to 1.83 at 9 M H_2SO_4, although these figures may be increased by an order of magnitude if 0.05 M Cl^- is also present in the aqueous phase.[144] Better extraction is possible using more basic phosphoryl compounds such as TOPO. This will extract UO_2^{2+} from sulfate media but, as a 0.1 M solution in cyclohexane, even TOPO only gives a $D_{U^{VI}}$ of 1 from 1 M H_2SO_4 compared with 10^3 from 1 M HNO_3. Since acid ore leaching processes commonly employ H_2SO_4, TBP is not widely used in the intermediate purification stage. However, where solutions of uranium in nitric acid are involved, TBP would be the reagent of choice because its high selectivity gives a purer product. Thus at the Forez (France) and Mouana (Republic of Gabon) plants[145] the uranium ore is leached using acidic sulfate media but the uranium is then precipitated and redissolved in nitric acid prior to TBP extraction. Nitric acid solutions also arise in the production of Rum Jungle (Australia) yellowcake[146] and are used in the final stages of uranium purification prior to fuel fabrication. Nitric acid is also the reagent primarily used in the reprocessing of irradiated fuels. Accordingly the extraction of UO_2^{2+} from nitrate media by TBP will be considered in more detail in Sections 65.2.3.1 and 65.2.4.3, which relate to these topics.

Among the processes involving tertiary amine or dialkyl phosphoric acid extractants the AMEX process has largely superseded the DAPEX and DPPA processes in the USA because of its higher selectivity. However, dialkyl phosphoric acid may still be used in cases where vanadium recovery is also required. The Eluex process developed in the USA, and its South African counterpart, Bufflex, involve the ion exchange treatment of a sulfuric acid leachate prior to solvent extraction purification. However, improvements in the solvent extraction stage have led to the elimination of the ion exchange step in the AMEX process and in the South African Purlex process[148] which has superseded Bufflex. The production of phosphoric acid from phosphate rock often leads to solutions containing low but significant concentrations of uranium. A process for its recovery by two stages of solvent extraction treatment has been described.[149] The first stage involves a mixture of mono- and di-(octylphenyl) phosphoric acids in an aliphatic diluent, Amsco 450, while the second uses a synergistic HDEHP/TOPO mixture in Amsco 450. Uranium recovery from phosphoric acid solutions by supported liquid membrane extraction using HDEHP/TOPO has also been described recently.[150] Process details and flowsheets for various yellowcake production plants may be found in the Proceedings of Conferences on Uranium Recovery and Solvent Extraction.[63–66]

65.2.2.2 Thorium

The principal resource minerals for thorium are Monazite, a rare earth phosphate, Thorite, $ThSiO_4$, and Thorianite or Uranothorianite, $(U, Th)O_2$, of which Monazite is the most important. Thorium minerals are mainly concentrated in sedimentary ores derived from the heavy refractory

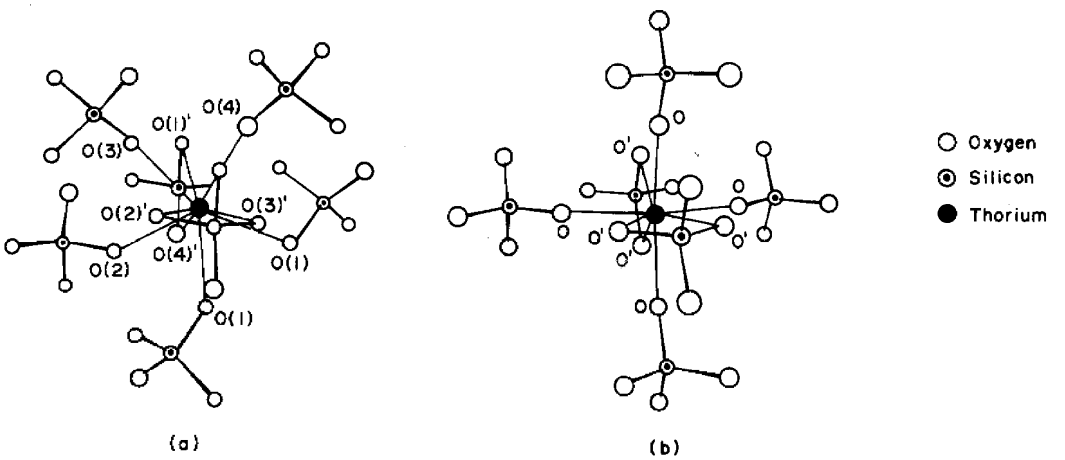


Figure 20 The thorium environments in (a) huttonite and (b) thorite. (Reproduced from M. Taylor and R. C. Ewing, *Acta Crystallogr.*, 1978, **B34**, 1074, with the permission of the International Union of Crystallography)

mineral fraction of a source rock. Beach sand placers in India, and along the coastlines of Brazil, Australia and Florida in the USA, provide examples of deposits which have Monazite contents of between 1 and 5%. The ThO_2 content of Monazite itself is some 8–10%, giving an overall thorium concentration in Monazite sands of 0.1–0.5%. Alluvial deposits containing Monazite may form in valleys as in Idaho in the USA, and in some cases thorium may be recovered from the barren leach liquors produced by uranium recovery. Solid state structural studies of thorium minerals have shown that Thorite is isostructural with Zircon,[151] $ZrSiO_4$, and Coffinite,[152] having an eight-coordinate thorium environment containing four monodentate and two bidentate SiO_4^{4-} ligands, as illustrated in Figure 20. Huttonite, $ThSiO_4$, was found[151] to be isostructural with Monazite, $LnPO_4$, where Ln^{3+} is mainly Ce^{3+} with La^{3+} and Nd^{3+}, having a nine-coordinate thorium environment containing five monodentate and two bidentate SiO_4^{4-} ligands, as also shown in Figure 20. This latter coordination geometry was broadly similar to that found in $Th_2(PO_3)_4^{4-}$ as its isostructural potassium[153] or sodium[154] salts. In this case the bidentate phosphate ligands were nonbridging while the monodentate ligands were involved in bridging between Th^{4+} ions.

The refractory nature of the thorium minerals necessitates a rather aggressive chemical treatment to release the thorium. As with uranium recovery, this is preceded by mechanical processing, or froth flotation, to concentrate the thorium-rich ore components and render them more susceptible to leaching. Acid or alkali leaching processes may be employed and the main features of each approach are summarized in Figures 21 and 22 respectively. The chemistry and process details of thorium recovery have been reviewed.[2,4,9,50] The acid leaching process is well developed historically but does not give complete separation of thorium from phosphorus. In recent times the alkali leaching process has thus become more widely adapted as an economic and effective separation method. To obtain material of acceptable purity for nuclear fuel fabrication, a final solvent extraction purification is necessary and this will be described in Section 65.2.3.2. However, unlike the case for uranium, precipitation techniques alone usually suffice for the preparation of the thorium concentrate.

(i) Alkali leaching

The alkali leaching process, shown in outline in Figure 21, involves the digestion of the dressed ore with hot sodium hydroxide solution to dissolve the phosphate present as Na_3PO_4 and produce a slurry of metal hydroxides according to equations (73) and (74), where Ln represents the oxidation state (III) lanthanide elements present. The mixture is then diluted at an elevated temperature and the solid metal hydroxides separated by filtration. On cooling, Na_3PO_4 crystallizes from the filtrate and the sodium hydroxide containing mother liquor may be recycled. The metal hydroxide mixture is next redissolved either in hydrochloric acid or in ammonium carbonate solution. The carbonate leaching process has the advantage of selectivity in that almost complete separation of thorium from the lanthanides may be achieved. The dissolution reactions which occur are summarized by equations (75) and (76). Although the structure of the $Th(CO_3)_3^{2-}$ ion is uncertain the complex $Na_6[Th(CO_3)_5]\cdot 12H_2O$ has been shown[155] to contain five bidentate CO_3^{2-} ligands disposed around the Th^{4+} ion to give a 10-coordinate distorted hexadecahedral ThO_{10} polyhedron. The U^{VI} present is also dissolved in the form of $(NH_4)_4[UO_2(CO_3)_3]$. Subsequently,

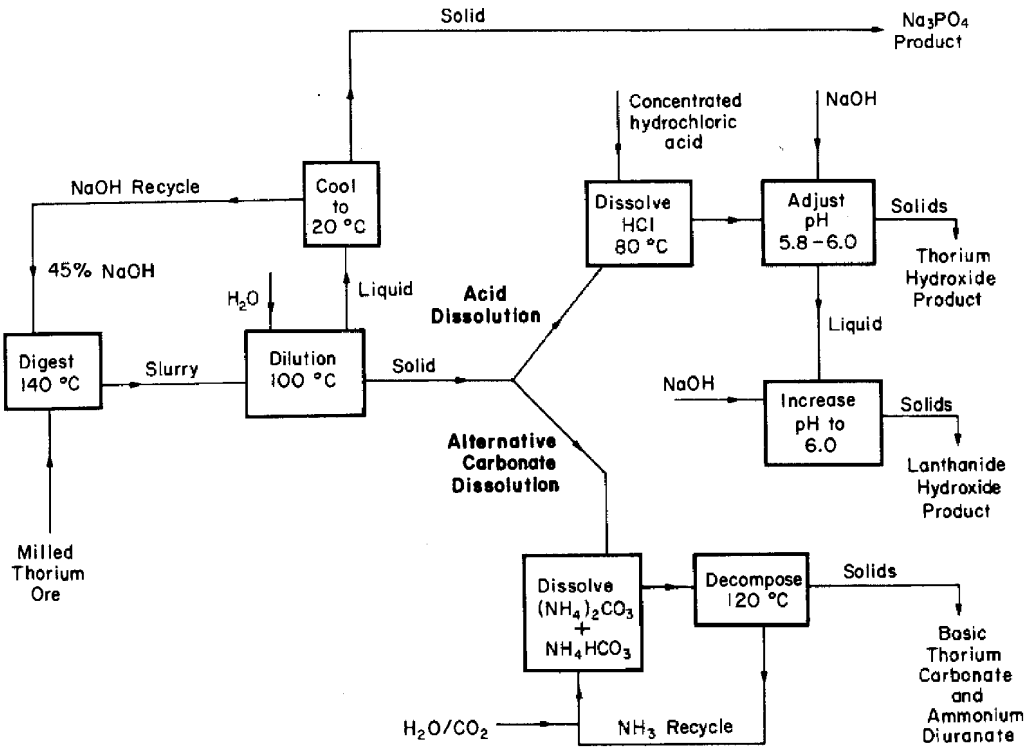


Figure 21 An outline flowsheet for the alkaline extraction of thorium from its ore

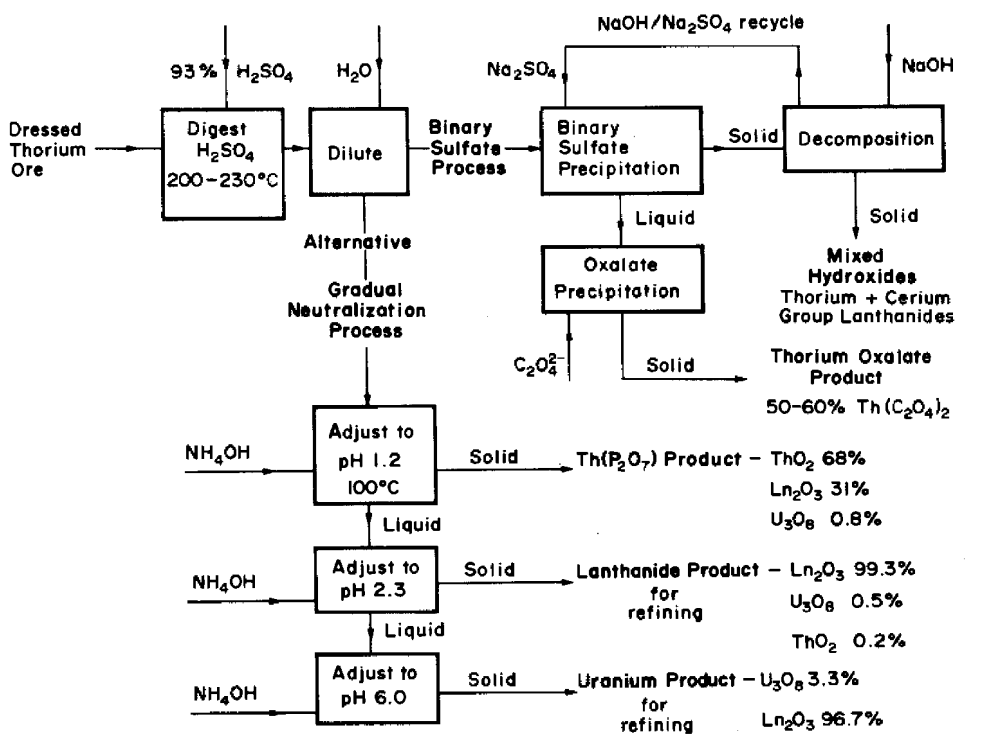


Figure 22 An outline flowsheet for the acidic extraction of thorium from its ore

basic thorium carbonate, along with some ammonium diuranate, may be precipitated by steam treatment which also liberates ammonia for recycle. The product from this process is lower in sulfate and phosphate than that obtained by hydrochloric acid treatment. In this acid dissolution method the pH of the solution produced is adjusted to between 5.8 and 6.0, under which conditions the thorium hydroxide product precipitates. The hydrolysis of Th^{4+} in media of ionic strength 1.0 has been shown[156] to proceed in five stages involving the hydrated species $Th(OH)^{3+}$, $Th_2(OH)_2^{6+}$, $Th_4(OH)_8^{8+}$ and $Th_6(OH)_{15}^{9+}$. More recent studies[157] carried out in media ranging from 0.5 to 3.0 M in $NaNO_3$ also indicated the existence of $Th_3(OH)_5^{7+}$ and showed that the extent of Th^{4+} hydrolysis increased with increasing thorium concentration, but decreased with increasing $NaNO_3$ concentration. Thorium hydrolysis in 3 M NaCl[158] and lower ionic strength 0.1 M KNO_3 media[29] has also been described. In this latter case, mono-, tetra- and hexa-nuclear species were identified but no evidence was obtained for dinuclear species. However, solid state structural studies have revealed the existence of a dinuclear hydroxy bridged $\{Th(\mu\text{-}OH)_2Th\}^{6+}$ moiety in $[Th_2(\mu\text{-}OH)_2(NO_3)_6]\cdot 8H_2O$.[159] Polymeric chains of hydroxy bridged $\{Th(OH)_2\}^{2+}$ units have also been found in $[Th(OH)_2(NO_3)_2]$ hydrate[160] and $[Th(OH)_2SO_4]$, which is isostructural with $[U(OH)_2SO_4]$.[161] Further increases in the pH of the solution remaining after separation of the thorium product causes the rare earth metals present to precipitate and the product so formed can be further processed as a source of lanthanide elements. The stability constants and solubility products of metal complexes of inorganic ligands, including the hydroxides of Th^{4+} and some Ln^{3+} ions, have recently been summarized by Hogfeldt.[162] Thermodynamic data on complexation in aqueous media have also been compiled by Kragten.[163]

$$Th_3(PO_4)_4 + 12NaOH \rightarrow 3Th(OH)_4 + 4Na_3PO_4 \quad (73)$$

$$LnPO_4 + 3NaOH \rightarrow 3Ln(OH)_3 + Na_3PO_4 \quad (74)$$

$$Th(OH)_4 + 3(NH_4)_2CO_3 \rightarrow (NH_4)_2Th(CO_3)_3 + 4NH_4OH \quad (75)$$

$$NH_4OH + NH_4HCO_3 \rightarrow (NH_4)_2CO_3 + H_2O \quad (76)$$

(ii) Acid leaching

In the acid leaching process,[2,50] outlined in Figure 22, the dressed ore is digested with hot concentrated sulfuric acid to dissolve the thorium present according to equations (77) and (78). The lanthanide elements are also dissolved according to equation (79), along with the uranium present. The leach liquor is then cooled and diluted. At 45 °C, thorium sulfate is more soluble than the lanthanide sulfates whose solubility decreases with increasing temperature. Some partial Ln/Th separation may thus be effected on the basis of these solubility differences. However, two general approaches may be adopted to obtain a more complete separation of thorium salts. The first method of gradual neutralization involves the adjustment of the diluted leach liquor pH to about 1.0, under which conditions thorium pyrophosphate, ThP_2O_7, is precipitated according to equation (80), along with about 5% of the lanthanides present. It is necessary at this stage to

$$Th_3(PO_4)_4 + 6H_2SO_4 \rightarrow 3Th(SO_4)_2 + 4H_3PO_4 \quad (77)$$

$$ThSiO_4 + 2H_2SO_4 \rightarrow Th(SO_4)_2 + SiO_2 + 2H_2O \quad (78)$$

$$2LnPO_4 + 3H_2SO_4 \rightarrow Ln_2(SO_4)_3 + 2H_3PO_4 \quad (79)$$

$$Th^{4+} + 2H_2PO_4^- \rightarrow ThP_2O_7 + H_2O + 2H^+ \quad (80)$$

maintain the lanthanide concentration in solution below 2% to avoid the precipitation of lanthanide sulfates. The product obtained is a thorium concentrate which contains roughly equal amounts of thorium and mixed lanthanides. The supernatant pH may subsequently be adjusted to 2.3 to precipitate lanthanide acid phosphates, $Ln_2(HPO_4)_3$, as a secondary product. The liquor from this stage may then be further treated to raise the pH to 6.0 and precipitate the remaining lanthanides and uranium, giving another product containing about 1% uranium. This method tends to distribute any uranium present throughout the three product streams. More effective separation may be achieved by the alternative method of binary sulfate precipitation. In this process the binary sodium–lanthanide sulfates are first precipitated by adding NaOH and Na_2SO_4 to the sulfuric acid leach liquors. The solubility of $Na_2SO_4\cdot Th(SO_4)_2\cdot 6H_2O$ is higher than that of the lanthanide salts so that the bulk of the thorium is carried forward in solution. The thorium may be precipitated in the next stage by the addition of oxalate to give a concentrate containing 50–60% $Th(C_2O_4)_2$ and about 6% lanthanide salts. The lanthanide binary sulfate precipitate can

be broken down with sodium hydroxide to give an $NaOH/Na_2SO_4$ liquor for recycle and a solid product containing lanthanide hydroxides and some thorium. The use of NH_4OH in place of NaOH to neutralize the sulfuric acid leach liquor to a pH of 0.6 in the initial stage of the process was claimed to reduce the proportion of thorium precipitated with the lanthanide binary sulfates.[164] Increasing the pH of the supernatant to 1.8 then precipitated a thorium product which had a Th : Ln ratio of 4 : 1. The binary sulfate precipitation method is preferred industrially to the gradual neutralization method and the sulfuric acid leaching process has been adopted by some plants in the USA. Elsewhere in the world, and in Tennessee in the USA, the sodium hydroxide leaching process has been used.[2]

(iii) Recovery from uranium processing

In regions where uranium ores also contain significant amounts of thorium it may be possible to extract this from barren uranium processing solutions. Solvent extraction treatment provides an effective means of recovering thorium and, as with uranyl solutions, cationic, anionic or neutral types of reagent can be used to extract Th^{4+} from aqueous media.[165] The dialkyl phosphate extractants are rather less selective than organoamines and their performance can be seriously impaired by Fe^{3+}. The primary alkylamines and straight-chain dialkylamines appear to be the most effective extractants for Th^{4+} from sulfuric acid solutions. A xylene solution of Primene JMT (**9**), for example, gives a distribution coefficient, D_{Th}, of over 10^4 from 0.1–1.0 M sulfuric

$$Bu^t—(CH_2—CMe_2)_4—NH_2$$

(**9**)

acid. In the case of di-*n*-octylamine (DOA) and di(tridecyl)amine as 0.1 M solutions in xylene, D_{Th} values in excess of 10^3 were obtained[166] for sulfuric acid concentrations below 0.1 M. The stoichiometry of Th^{4+} extraction from sulfate media by DOA as a 0.1 M solution in benzene was found[167] to follow equation (81) under conditions of low acidity, and equation (82) at higher acidity. The extracted species was shown to have the composition $(DOAH)_6Th(SO_4)_5(H_2O)_3$. The

$$Th(SO_4)_{2(aq)} + 3(DOAH)_2SO_{4(org)} \rightleftharpoons \{(DOAH)_2SO_4\}_3Th(SO_4)_{2(org)} \quad (81)$$

$$Th(SO_4)_{2(aq)} + 6DOAH \cdot HSO_{4(org)} \rightleftharpoons \{(DOAH)_2SO_4\}_3Th(SO_4)_{2(org)} + 3H_2SO_{4(aq)} \quad (82)$$

structure of the thorium coordination sphere is uncertain but the solid state structure of $K_4[Th(SO_4)_4]_2 \cdot H_2O$ has been shown to contain nine-coordinate Th^{4+} with a tri-square-capped trigonal prismatic ThO_9 geometry. The four SO_4^{2-} anions were coordinated as one monodentate, one bidentate and two bidentate and bridging to other Th^{4+} ions. The variation of D_{Th} with acid concentration is shown in Figure 23. The shape of these curves suggested that, at low acidity, increasing sulfate concentrations gave rise to a salting out effect and increased D_{Th}, while at higher acidity, H_2SO_4 competed with Th^{4+} for the extractant in the organic phase. The value of D_{Th} decreased with temperature and the enthalpy of extraction was estimated as -8.8 and -6.3 kJ mol^{-1} for 0.1 M and 0.25 M sulfuric acid solutions respectively. On the basis of these figures it was proposed that hydrogen bonding played a major role in stabilizing the extracted species. Amine extraction with di-*n*-decylamine has been used[169] to determine the stepwise formation constants of $Th(SO_4)_3^{2-}$ and $Th(SO_4)_4^{4-}$ according to equations (83) and (84). These were found to be 5.7 ± 1.2 and 0.009 ± 0.003 respectively for zero ionic strength.

$$Th(SO_4)_2 + SO_4^{2-} \rightleftharpoons Th(SO_4)_3^{2-} \quad (83)$$

$$Th(SO_4)_3^{2-} + SO_4^{2-} \rightleftharpoons Th(SO_4)_4^{4-} \quad (84)$$

The extraction of Th^{4+} from nitric acid solutions by organoamines has been studied by a number of workers, although these reagents are rather ineffective for this purpose. The values of D_{Th} in the 10% TOA in xylene/HNO_3 system, for example, are less than 1 over the range 1–10 M HNO_3 and are an order of magnitude less than those obtained for Np^{IV} and some 50 times less than for Pu^{IV}.[170] Sato has shown that, for benzylalkylamines as 0.1 M solutions in benzene, the secondary amines are superior to the tertiary amines in extracting Th^{4+} from sulfuric acid.[171] The value of D_{Th} was a maximum at 0.1 M H_2SO_4 and was greater than 100 for *N*-benzyldodecylamine (BDA), *ca.* 18 for *N*-benzyl(2-ethylhexyl)amine (BEHA), but only *ca.* 2 for *N,N*-dibenzyldodecylamine (DBDA) and *ca.* 0.3 for *N*-benzyldidodecylamine (BDDA). However, for nitric acid solutions with 0.2 M organoamine in xylene the reverse was found[172] in that maximum values of D_{Th} for DDA and BEHA were less than 0.3 at 10 M HNO_3, while for the tertiary amines BDDA and *N*-benzyldi(2-ethylhexyl)amine maximum values in the range 1.5–2 were obtained at *ca.* 5 M

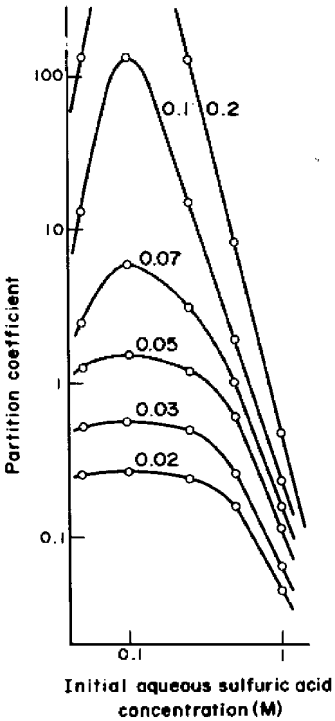


Figure 23 The extraction of Th^{IV} from H_2SO_4 by DOA in benzene.[179] The curves are labelled with DOA concentration (M)

HNO_3. The extraction of Th^{4+} from nitrate media was thought to involve $Th(NO_3)_5^-$ as an intermediate with $Th(NO_3)_6^{2-}$ being the preferentially extracted species.[173] More recent work[174] supports this formulation of the extracted complex and establishes the extraction reaction shown in equation (85) for 0.1 M tridecylamine (TDA) in benzene. The solid state structure of $Mg[Th(NO_3)_6]\cdot 8H_2O$ has been shown[175] to contain Th^{4+} coordinated to six bidentate NO_3^- ligands to give an irregular icosohedral ThO_{12} coordination sphere. This contrasts with the 11-coordinate arrangement of four bidentate NO_3^- and three H_2O ligands found[176] in $[Th(NO_3)_4(H_2O)]\cdot 2H_2O$.

$$Th^{4+}_{(aq)} + 4NO_3^-{}_{(aq)} + 2TDA\cdot HNO_{3(org)} \rightleftharpoons (TDAH)_2Th(NO_3)_{6(org)} \quad (85)$$

Amine reagents also extract thorium from carbonate solutions and the use of a primary amine, RNH_3Cl, where $R = C_{10}$ to C_{13} alkyl, as a 20% solution in kerosene allowed the concentrations of impurities in the extracted thorium to be reduced by factors of 33.8 for U^{VI}, 111.4 for Mo^{VI}, 18.9 for Zr^{IV} and 6167 for Mg^{II}.[177] The extracted thorium species was shown to be of the composition $(RNH_3)_4Th(CO_3)_4(H_2O)_x$. Di(tridecyl)amine has been used to extract thorium from barren uranium process liquors in the Blind River plant in Canada[147] and flowsheets for the recovery of lanthanides, UO_3 and high-purity $Th(SO_4)_2$ from the Elliot Lake area in Ontario using Primene/isodecanol have been described.[178]

The extraction of Th^{4+} from sulfuric acid media by alkyl phosphoric acid reagents has been studied[165] and for HDEHP the reaction given by equation (86) was proposed.[118] Subsequent work[179] indicated that, while this reaction applied for HDEHP concentrations above 0.03 M with 0.25–0.5 M H_2SO_4, at H_2SO_4 concentrations below 0.1 M polymeric species were also extracted according to equation (87). The overall extraction stoichiometry was thus given by equation (88) where $n > 1$. The variation of D_{Th} with HDEHP and sulfuric acid concentration is illustrated in Figure 24. At higher pH values, extraction according to equations (89) and (90) was proposed[180]

$$Th^{4+}_{(aq)} + 4(HDEHP)_{2(org)} \rightleftharpoons Th\{H_4(DEHP)_8\}_{(org)} + 4H^+_{(aq)} \quad (86)$$

$$Th\{H_4(DEHP)_8\}_{(org)} + Th^{4+}_{(aq)} + 2(HDEHP)_{2(org)} \rightleftharpoons Th_2\{H_4(DEHP)_{12}\}_{(org)} + 4H^+_{(aq)} \quad (87)$$

$$nTh^{4+}_{(aq)} + (2n+2)(HDEHP)_{2(org)} \rightleftharpoons Th_n\{H_4(DEHP)_{2(2n+2)}\}_{(org)} + 4nH^+_{(aq)} \quad (88)$$

$$Th^{4+}_{(aq)} + 2(HDEHP)_{2(org)} \rightleftharpoons Th(DEHP)_{4(org)} + 4H^+_{(aq)} \quad (89)$$

$$ThO^{2+}_{(aq)} + (HDEHP)_{2(org)} \rightleftharpoons ThO(DEHP)_{2(org)} + 2H^+_{(aq)} \quad (90)$$

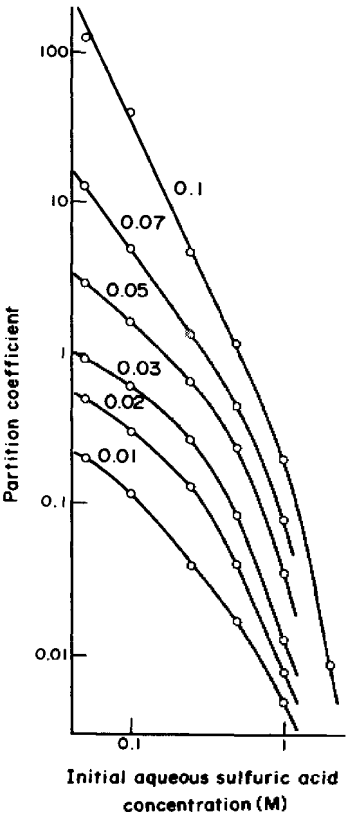


Figure 24 Extraction of Th^{IV} from H_2SO_4 by HDEHP in kerosene.[179] The curves are labelled with HDEHP concentration (M)

to account for the observed reaction stoichiometry, the absence of sulfate in the organic phase and the lack of IR evidence for $Th(OH)^{3+}$ species in the organic phase. These results were not in accord with those of Sato, possibly because of the higher pH of the systems studied. Higher values of D_{Th} were obtained[181] for H_2SO_4 solutions of high acidity if 0.7 M HDEHP in xylene was used as the extractant. Addition of HCl to the aqueous phase further increased D_{Th} at H_2SO_4 concentrations of 9 M and D_{Th} values of the order of 10^2 could be achieved over the H_2SO_4 concentration range 1–10 M.

The extraction of tracer levels of Th^{4+} from HNO_3 by HDEHP was proposed[182] to occur according to equations (91) and (92), while for Th^{4+} concentrations of *ca.* 10^{-2} M in 0.1–4 M nitrate at pH 1.6 equations (93)–(95) were proposed[180] to describe the extraction reactions occurring. At high acidities, equation (96) was found[183] to describe the extraction. The variation of D_{Th} with HDEHP and HNO_3 concentrations is shown in Figure 25. In the extraction of Th^{4+} from aqueous HNO_3 or HCl using HDBP, equation (97) was said to apply.[184] The proposed extracted species defined in equations (92), (93) and (97) appear to represent only differing degrees of solvation of $Th(NO_3)X_3$ by HX where $X^- = DEHP^-$ or DBP^-. In methyl isobutyl ketone (MIBK) diluent it was found[184] that HDBP extracted $Th(NO_3)_4$ at HDBP concentrations below 10^{-5} M, $Th(NO_3)_2(DBP)_2$ at HDBP concentrations between $10^{-4.6}$ and $10^{-3.5}$ M and

$$Th^{4+}_{(aq)} + 3(HDEHP)_{2(org)} \rightleftharpoons Th\{H_2(DEHP)_6\}_{(org)} + 4H^+_{(aq)} \quad (91)$$

$$Th(NO_3)^{3+}_{(aq)} + 3(HDEHP)_{2(org)} \rightleftharpoons Th(NO_3)\{H_3(DEHP)_6\}_{(org)} + 3H^+_{(aq)} \quad (92)$$

$$Th(NO_3)^{3+}_{(aq)} + \tfrac{3}{2}(HDEHP)_{2(org)} \rightleftharpoons Th(NO_3)(DEHP)_{3(org)} + 3H^+_{(aq)} \quad (93)$$

$$Th(NO_3)_2^{2+}{}_{(aq)} + (HDEHP)_{2(org)} \rightleftharpoons Th(NO_3)_2(DEHP)_{2(org)} + 2H^+_{(aq)} \quad (94)$$

$$Th^{4+}_{(aq)} + 2(HDEHP)_{2(org)} \rightleftharpoons Th(DEHP)_{4(org)} + 4H^+_{(aq)} \quad (95)$$

$$Th^{4+}_{(aq)} + 4NO_3^-{}_{(aq)} + (HDEHP)_{2(org)} \rightleftharpoons Th(NO_3)_4 \cdot 2HDEHP_{(org)} \quad (96)$$

$$Th^{4+}_{(aq)} + NO_3^-{}_{(aq)} + 5HDBP_{(aq)} \rightleftharpoons Th(NO_3)(DBP)_3(HDBP)_{2(org)} + 3H^+_{(aq)} \quad (97)$$

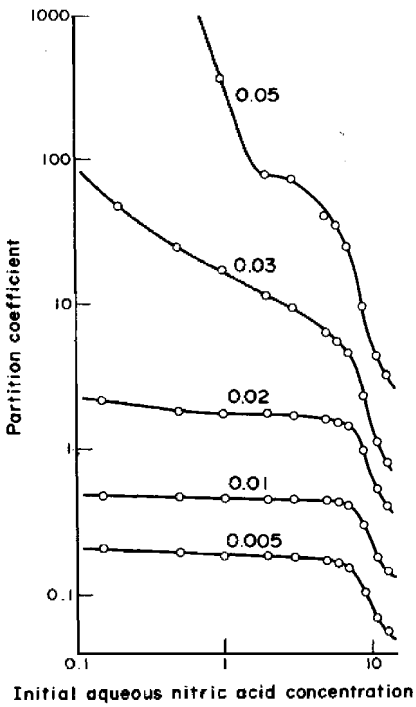


Figure 25 Extraction of Th^{IV} from HNO_3 by HDEHP in kerosene.[183] The curves are labelled with HDEHP concentration (M)

$Th(NO_3)(DBP)_3$ above $10^{-3.4}$ M HDBP. TBP was found to act as an antagonist in such systems by competing with Th^{4+} for the extractant. In the monomerizing diluent 2-ethylhexanoic acid (HEHA) the extraction stoichiometry of Th^{4+} by HDEHP was given[185] by equation (98) with $Th\{H(DEHP)_2\}\{(DEHP)(HEHA)\}_3$ being proposed as the extracted complex; D_{Th} values of *ca.* 7×10^4 were obtained with this system. The use of sterically hindered dialkyl phosphoric acid, $(RO)_2P(O)OH$, extractants has been investigated and values of D_{Th} of 40, compared with 10^5 for $D_{U^{VI}}$, were obtained.[186] The tendency of inorganic anions to extract with the Th^{4+} according to equation (99) was found to increase with decreasing extraction efficiency of the $(RO)_2P(O)OH$.

$$Th^{4+}_{(aq)} + 5HDEHP_{(org)} \rightleftharpoons Th\{H(DEHP)_5\}_{(org)} + 4H^+_{(aq)} \quad (98)$$

$$Th^{4+}_{(aq)} + 2NO_3^-{}_{(aq)} + 2\{(RO)_2P(O)OH\}_{2(org)} \rightleftharpoons Th(NO_3)_2\{H_2[(RO)_2PO_2]_4\}_{(org)} + 2H^+_{(aq)} \quad (99)$$

Anions such as NO_3^- were thought to be able to compete more effectively with the more sterically hindered extractants for Th^{4+} coordination sites. The extraction of Th^{4+} by monoalkyl phosphoric acid[187] and dialkyl phosphonic acids[188] has also been reported.

Neutral extractants for Th^{4+} include MIBK, hexanol, Butex, TBP and TOPO.[165] In industry, TBP is the most widely used of these and its applications, for example in the Thorex process for separating uranium and thorium, will be discussed in Sections 65.2.3.2 and 65.2.4.3(iv). However, TOPO is a more powerful extractant for Th^{4+} than TBP. At low (<0.01 M) Th^{4+} and HNO_3 concentrations the species extracted from nitric acid by TOPO in cyclohexane was found[189] to be $Th(NO_3)_4 \cdot 3TOPO$, but at higher acidities nitric acid was also extracted. This may result from the formation of adducts $Th(NO_3)_4 \cdot nHNO_3 \cdot 3TOPO$ or from the direct extraction of $H_2[Th(NO_3)_6]$. The trisolvate formulation of the extracted species was confirmed in another study,[190] which showed a maximum value for D_{Th} in the nitric acid concentration range 0.3–0.4 M. Values of D_{Th} in excess of 10^2 were found at this acidity using 0.2 M TOPO in kerosene; these fell to *ca.* 7 for 0.1 M TOPO. The enthalpy of extraction of Th^{4+} from 0.3 M HNO_3 using 0.06 M TOPO was found to be 24.3 kJ mol^{-1}. Dibutyl butylphosphonate also extracts Th^{4+} from nitric acid as a trisolvate, $Th(NO_3)_4 \cdot 3DBBP$.[191] A detailed investigation[192] of UO_2^{2+} and Th^{4+} extraction from HNO_3 by TBP, DBBP and more sterically hindered neutral phosphonates and phosphinates, over the temperature range 0–50 °C, showed that the steric bulk of the extractant has a major effect on Th^{4+} extraction, but has little influence on UO_2^{2+} extraction. Such data provide a basis for developing more effective specialized extractants for Th^{4+}/UO_2^{2+} separation. Unlike the neutral

phosphoryl reagents, thorium extraction by *n*-hexanol (ROH) has been found[193] to involve a hydrated tetrasolvate according to equation (100). In the Butex/aqueous nitric acid system the value of D_{Th} was found[194] to increase with increasing HNO_3 concentration to a maximum of *ca.*

$$Th^{4+}_{(aq)} + 4NO_3^-{}_{(aq)} + 4ROH_{(org)} + 5H_2O_{(aq)} \rightleftharpoons Th(NO_3)_4 \cdot 4ROH \cdot 5H_2O_{(org)} \quad (100)$$

25 at 7 M HNO_3. This value was substantially less than for other oxidation state (IV) actinides, which gave partition coefficients decreasing in the order Pu > Np > U > Th.

65.2.3 Nuclear Fuel Preparation

The uranium and thorium ore concentrates received by fuel fabrication plants still contain a variety of impurities, some of which may be quite effective neutron absorbers. Such impurities must be almost completely removed if they are not seriously to impair reactor performance. The thermal neutron capture cross sections of the more important contaminants, along with some typical maximum concentrations acceptable for fuel fabrication, are given in Table 9. The removal of these unwanted elements may be effected either by precipitation and fractional crystallization methods, or by solvent extraction. The former methods have been historically important but have now been superseded by solvent extraction with TBP. The thorium or uranium salts so produced are then of sufficient purity to be accepted for fuel preparation or uranium enrichment. Solvent extraction by TBP also forms the basis of the Purex process for separating uranium and plutonium, and the Thorex process for separating uranium and thorium, in irradiated fuels. These processes and the principles of solvent extraction are described in more detail in Section 65.2.4, but the chemistry of UO_2^{2+} and Th^{4+} extraction by TBP is considered here.

Table 9 Neutron Absorbing Impurities in Uranium[50]

Element	*Thermal neutron capture cross section* (barn)	*Typical maximum permitted concentration* (p.p.m.)
Aluminum	0.215	20
Boron	750	0.2
Carbon	0.0045	600
Nitrogen	0.075	100
Silicon	0.13	40
Chromium	2.90	25
Iron	2.43	150
Cobalt	34.8	25
Nickel	4.50	80
Cadmium	2400	0.2

65.2.3.1 Final purification of uranium

The purification of uranium by precipitation may involve the formation of insoluble oxalate or peroxide complexes.[50] In the oxalate method the ore concentrate is dissolved in nitric acid to give a uranyl nitrate solution from which uranyl oxalate is precipitated according to equation (101), leaving the bulk of the impurities in solution. This approach is favoured over dissolution in hydrochloric acid and reduction to U^{IV} prior to $U(C_2O_4)_2$ precipitation since it is simpler and

$$UO_2(NO_3)_2 + H_2C_2O_4 \rightarrow UO_2(C_2O_4)\downarrow + 2HNO_3 \quad (101)$$

consumes less oxalic acid.[50] The solid state structure of $UO_2(C_2O_4) \cdot 3H_2O$ has been determined[194] and contains chains of approximately pentagonal bipyramidally coordinated U^{VI} bridged by bidentate $C_2O_4^{2-}$ ligands, as illustrated in Figure 26. The structures of three other uranyl oxalate species have been investigated[195] by Alcock and all contain U^{VI} in a distorted pentagonal bipyramidal coordination environment. The oxalate precipitate may be calcined to give a UO_2 product according to equation (102).

$$UO_2(C_2O_4) \cdot 4H_2O \xrightarrow{\text{heat}} UO_2 + 2CO_2\uparrow + 4H_2O \quad (102)$$

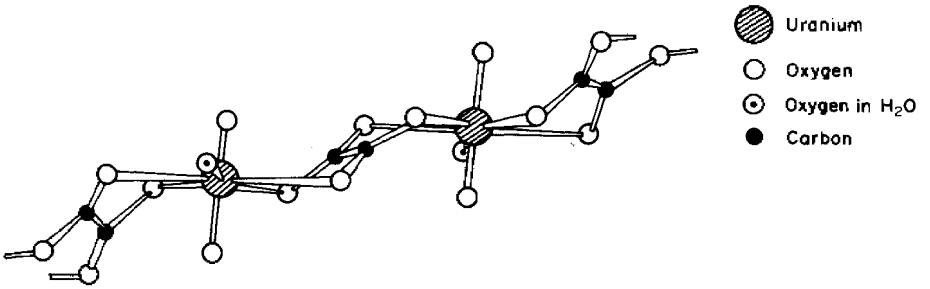
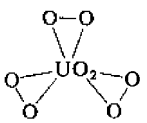


Figure 26 The structure[194] of the polymeric chain in $[UO_2(H_2O)(C_2O_4)]$

The peroxide method involves the precipitation of uranyl peroxide by addition of H_2O_2 to uranyl nitrate solutions according to equation (103). Below 50 °C, $UO_4{\cdot}4H_2O$ precipitates, while

$$UO_2(NO_3)_2 + H_2O_2 + 4H_2O \rightarrow UO_4{\cdot}4H_2O\downarrow + 2HNO_3 \quad (103)$$

above 70 °C, $UO_4{\cdot}2H_2O$ precipitates.[196] The solid state structure of $Na_4[UO_2(O_2)_3]$ (**10**), containing approximately hexagonal bipyramidal U^{VI}, has been determined.[197] The peroxide O—O distance was 1.5 Å and the U—O peroxide and U=O oxo distances were 2.28 and 1.86 Å respectively. A



(**10**)

purification process involving the formation of soluble uranyl carbonate complexes, thereby removing impurities as insoluble hydroxides, has been used in Port Hope, Canada. However, this process is complicated and costly and has now been discontinued.

The purification of uranium by fractional crystallization involves repeated recrystallizations of $UO_2(NO_3)_2$ from water or nitric acid, three usually being sufficient. The composition of the crystalline product may range from $UO_2(NO_3)_2{\cdot}2H_2O$ to $UO_2(NO_3)_2{\cdot}6H_2O$ depending upon the temperature, acidity and uranyl nitrate concentration of the solution.[198]

In the solvent extraction purification of the uranium ore concentrate, TBP is the extractant of choice although, in the past, Butex, diethyl ether and MIBK have also been used for this purpose. The uranium ore concentrate is first dissolved in nitric acid to produce a solution of uranyl nitrate from which insoluble impurities are separated. The consumption of nitric acid in this step will depend upon the nature of the concentrate, as shown in equations (104)–(109). Many impurities

$$UO_3 + 2HNO_3 \rightarrow UO_2(NO_3)_2 + H_2O \quad (104)$$

$$U_3O_8 + 8HNO_3 \rightarrow 3UO_2(NO_3)_2 + 4H_2O + 2NO_2 \quad (105)$$

$$3U_3O_8 + 20HNO_3 \rightarrow 9UO_2(NO_3)_2 + 10H_2O + 2NO \quad (106)$$

$$UO_2 + 4HNO_3 \rightarrow UO_2(NO_3)_2 + 2NO_2 + 2H_2O \quad (107)$$

$$MU_2O_7 + 6HNO_3 \rightarrow 2UO_2(NO_3)_2 + M(NO_3)_2 + 3H_2O; \quad M^{2+} = Mg^{2+} \text{ or } 2Na^+ \quad (108)$$

$$Na_2(UO_2)_2(V_2O_8) + 6HNO_3 \rightarrow 2UO_2(NO_3)_2 + 2NaNO_3 + 2HVO_3 + 2H_2O \quad (109)$$

are also dissolved and difficulties may arise if phosphate or vanadate are present, owing to the low solubilities of $NaUO_2VO_4$ and uranyl phosphates in HNO_3. The presence of Fe^{3+} can inhibit uranyl phosphate precipitation. The $UO_2(NO_3)_2$ solution is next contacted with TBP in odourless kerosene (OK) diluent. The oxidation state (I), (II) or (III) impurities are at most only poorly extracted by TBP whilst UO_2^{2+} is readily extracted according to the overall reaction given by equation (110).[200] This process is complicated by the extraction of HNO_3 by TBP to form mainly

$$UO_2^{2+}{}_{(aq)} + 2NO_3^-{}_{(aq)} + 2TBP_{(org)} \rightleftharpoons UO_2(NO_3)_2{\cdot}2TBP_{(org)} \quad (110)$$

$TBP{\cdot}HNO_3$, but at HNO_3:TBP mole ratios of less than 0.5, $(TBP)_2{\cdot}HNO_3$ is also formed, while at high acidities, $TBP(HNO_3)_2$ forms.[201–204] The variation of $D_{U^{VI}}$, and of D_{Th}, with nitric acid and TBP concentrations is illustrated in Figure 27.[205] The value of $D_{U^{VI}}$ reaches a maximum at

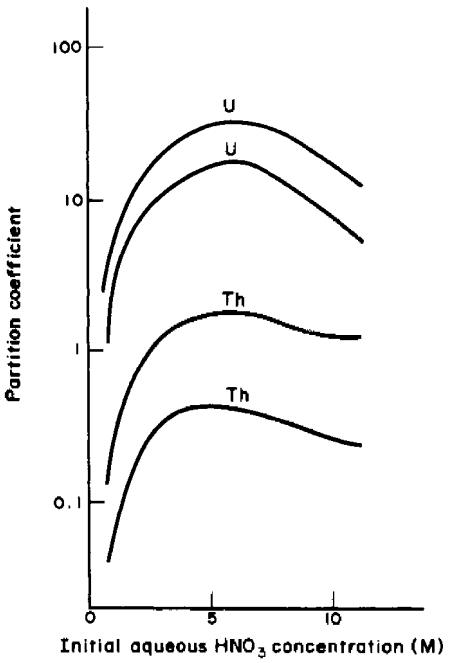


Figure 27 The extraction of U^{VI} and Th^{IV} from HNO_3 by TBP in kerosene. The upper curves of each pair are for 19.9% and the lower 9.9% TBP concentration[205]

ca. 6 M HNO_3 and under these conditions 97% UO_2^{2+} extraction from a 10 g dm^{-3} solution of $UO_2(NO_3)$ has been reported using a 19 v/o solution of TBP.[206] At low aqueous HNO_3 concentrations an increase in acidity, and thus nitrate concentration, promotes the complexation of UO_2^{2+} by nitrate to form neutral extractable species. However, at higher aqueous acidities the organic phase nitric acid concentration is also increased, reducing the free TBP concentration. The interplay of these processes produces a maximum in the plot of $D_{U^{VI}}$ *versus* HNO_3 concentration.[207] The absorptions at 1183 and 940 cm^{-1}, attributable to $\nu_{P=O}$ and $\nu_{U=O}$ respectively, in the IR spectrum of $[UO_2(NO_3)_2(TBP)_2]$ in the organic phase were found to obey the Beer-Lambert law and to allow quantitative determination of this complex.[208] Thermodynamic data on U^{VI} extraction by TBP have been obtained[204] and a value of -21 ± 2.1 kJ mol^{-1} assigned[209,210] to the enthalpy of extraction of $UO_2(NO_3)_2$ from aqueous solutions of zero acidity into TBP in a hydrocarbon diluent. The overall formation constant for $UO_2(NO_3)_2$ itself has been given as $\log \beta_2 = -1.7$ in aqueous nitric acid media.[211]

The mechanism of uranium transfer from the aqueous to the organic phase has also been investigated.[212-214] The migration of the UO_2^{2+} containing species to and from the interface involves diffusion and convection, the latter being stimulated by dissipation of the enthalpy of the extraction process. The activation energy for the diffusion of $[UO_2(NO_3)_2(TBP)_2]$ in a hydrocarbon diluent was evaluated[212] as 24 kJ mol^{-1}. At the interface, TBP is added to charged or neutral UO_2^{2+} complexes and NO_3^- may also bind to cationic species at this stage. No clear sequence of ligand addition was found, nor evidence for two independent reaction sequences transferring UO_2^{2+} in opposite directions. The reactions shown in equations (111) and (112) were

$$UO_2(NO_3)TBP^+ + UO_2(NO_3)(TBP)_2^+ \rightleftharpoons [UO_2(NO_3)_2(TBP)_2] + UO_2 \cdot TBP^{2+} \quad (111)$$

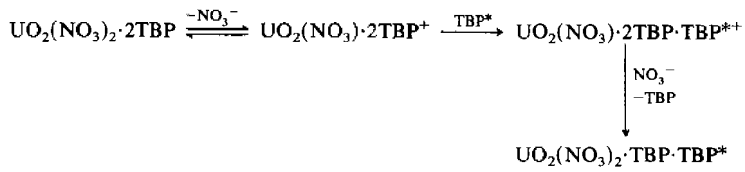
$$UO_2(NO_3)_2 \cdot TBP + UO_2(NO_3)(TBP)_2^+ \rightleftharpoons [UO_2(NO_3)_2(TBP)_2] + UO_2(NO_3)TBP^+ \quad (112)$$

involved in the formation of the interfacial complex whose concentration followed a Langmuir isotherm. The overall uranium transfer rate was governed by the rates of desorption of the interfacial complex into the aqueous or organic phases, and the rate of transfer from the aqueous to the organic phase was found to be some two orders of magnitude faster than the reverse process.[213] The rate constant for U^{VI} transfer into the organic phase increased with increasing TBP concentration, while the reverse transfer rate was very dependent on aqueous nitrate concentration. This difference between the forward and reverse rates indicated an activation energy for the process which was similar to the heat of reaction of $UO_2(NO_3)_2$ with TBP.[214] In a related system, the ligand exchange reactions of $[UO_2L_5]^{2+}$, where $L = (EtO)_3P{=}O$ or $(MeO)_3P{=}O$, have

been studied[215] in CD_2Cl_2 solutions by NMR techniques and a *D* or I_d reaction mechanism proposed. The charge density in $[UO_2L_5]^{2+}$, as seen by L, was found to lie between that in $[AlL_6]^{3+}$ and $[ML_6]^{2+}$, where M is a first-row *d*-block transition metal. The exchange of TBP itself in acetonitrile solution according to equation (113) was found[216] to be catalyzed by H_2O but inhibited

$$UO_2(NO_3)_2{\cdot}2TBP + TBP^* \rightleftharpoons UO_2(NO_3)_2{\cdot}TBP{\cdot}TBP^* + TBP \quad (113)$$

by NO_3^-. In low dielectric constant media the reaction proceeded *via* a $UO_2(NO_3)_2{\cdot}3TBP$ intermediate, but in high dielectric constant solvents the reaction proceeded according to Scheme 4, the fast pre-equilibrium step involving NO_3^- dissociation being suppressed by NO_3^- in accord with the earlier study.[214]



Scheme 4

The solid state structures of $[UO_2(NO_3)_2(H_2O)_2]{\cdot}4H_2O$[217-219] and $[UO_2(NO_3)_2\{(EtO)_3P{=}O\}_2]$[220] have been determined and are similar to those of $[UO_2(NO_3)_2(R_3P{=}O)_2]$, where R = Bu^n[221] or Ph,[222] $[UO_2(NO_3)_2(THF)_2]$,[223] where THF = tetrahydrofuran, and $Rb_2[UO_2(NO_3)_4]$.[224] All involve uranium in an approximately hexagonal bipyramidal coordination environment with two *trans* monodentate ligands and two bidentate NO_3^- ligands in an equatorial plane around the *trans* dioxo UO_2^{2+} ion, as illustrated in Figure 28. The structure of $Rb[UO_2(NO_3)_3]$ is also hexagonal bipyramidal but contains three bidentate NO_3^- ligands.[225,226] A typical uranium purification process, such as that operated at the Springfields Works in the UK,[199] might utilize 20–30 v/o TBP/OK as the extractant with an initial aqueous phase U^{VI} concentration of 200–230 g dm^{-3} in *ca.* 3 M HNO_3. The high U^{VI} concentration strongly suppresses the extraction of Th^{4+}, which might otherwise pass through with the uranium stream.

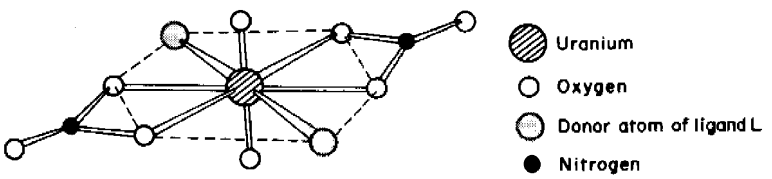


Figure 28 The generalized structure of the compounds $[UO_2(NO_3)_2L_2]$ in which L = H_2O,[217-219] $(EtO)_3PO$,[220] Bu_3^nPO,[221] Ph_3PO,[222] tetrahydrofuran[223] and NO_3^-[224]

The loaded organic phase is next contacted with dilute HNO_3 or water, which scrubs out residual impurities along with HNO_3 and some uranium. The aqueous scrub liquor is recycled to the extraction section to recover the uranium. The loaded organic phase containing 80–100 g dm^{-1} U^{VI} is then heated to 50–65 °C, which assists the back extraction, and contacted with demineralized water to give a pure aqueous uranyl nitrate product stream and a barren solvent phase for recycle. The product solution might contain *ca.* 100 g dm^{-1} U^{VI} while the aqueous raffinate from the first extraction may contain *ca.* 0.1 g dm^{-1} U^{VI}. The concentrations of boron and cadmium in the solid $UO_2(NO_3)_2{\cdot}6H_2O$ product obtained by evaporation of and crystallization from the product solution will be 0.2 p.p.m. or less.

65.2.3.2 Final purification of thorium

As with uranium, thorium may be purified by fractional crystallization methods.[50] The solubility of $Th(SO_4)_2{\cdot}9H_2O$ in water at 0 °C is 0.002 M, rising to 0.006 M at 45 °C. The solubility of the lanthanide sulfates at 0 °C is typically some two orders of magnitude higher but falls off sharply with increasing temperature. The crystallization of $Th(SO_4)_2{\cdot}9H_2O$ at 0 °C thus provides a means of separating thorium from the lanthanides. An alternative approach is to exploit the low solubility of the double salt of $Th(SO_4)_2$ with K_2SO_4. In a 0.35 M K_2SO_4 solution the salt $3.5K_2SO_4{\cdot}Th(SO_4)_2$ is only soluble to the extent of 3×10^{-5} M and may be selectively precipitated from solutions

containing lanthanide sulfates. Precipitation of ThF_4 or $Th(C_2O_4)_2 \cdot 6H_2O$ represent alternative separation methods and, in the oxalate system, further purification may be achieved by the selective dissolution of thorium in excess oxalate according to equation (114). The overall stability constants of Th^{4+} oxalate complexes have been measured as $\beta_1 = 7.20 \times 10^7$, $\beta_2 = 1.31 \times 10^{14}$ and $\beta_3 = 8.69 \times 10^{19}$ in $HClO_4$–$NaClO_4$ media of ionic strength 1.0.[227] Subsequent hydrolysis of the soluble complexes with NaOH affords a solid thorium hydroxide product. All the above processes require repeated solid–liquid separations to give a high-purity product and solvent extraction processing offers substantial advantages in cost and product quality.

$$Th(C_2O_4)_2 + 2(NH_4)_2C_2O_4 \rightleftharpoons (NH_4)_4[Th(C_2O_4)_4] \quad (114)$$

$$Th^{4+}{}_{(aq)} + 4NO_3^-{}_{(aq)} + 2TBP_{(org)} \rightarrow Th(NO_3)_4 \cdot 2TBP_{(org)} \quad (115)$$

The extractant of choice for thorium purification is TBP. The variation of D_{Th} with TBP and nitric acid concentration was illustrated in Figure 27[205] and, for a given TBP and HNO_3 concentration, D_{Th} was some 10–50 times less than $D_{U^{VI}}$. The extracted species was found[209,205,228] to be $Th(NO_3)_4 \cdot 2TBP$, formed according to equation (115). The solid state structure of the related compound $[Th(NO_3)_4(Ph_3P{=}O)_2]$ has been determined[229] and contains 10-coordinate Th^{4+} with four bidentate nitrate and two *trans* $Ph_3P{=}O$ ligands disposed in a distorted octahedral geometry around Th^{4+}. This compound is isostructural with its Ce^{4+} analogue.[230] Kinetic studies[214] have shown that the rate controlling step in Th^{4+} extraction by TBP was associated with chemical reactions at the interface. The rate of transfer into the organic phase was increased by increasing TBP concentrations, but the rate of the reverse transfer to the aqueous phase was suppressed by increasing aqueous nitrate concentrations. The extraction of Th^{4+} from 4 M $NaNO_3$ solutions by 5 v/o TBP/diluent mixture was found to be little influenced by changes in diluent from saturated to aromatic hydrocarbons or to halocarbons.[231] However, the solubility of $Th(NO_3)_4 \cdot 2TBP$ in the organic phase is limited so that the choice of diluent for a process may be important. In 35 v/o TBP/OK, for example, a third phase forms if the $Th(NO_3)_4 \cdot 2TBP$ concentration exceeds 0.2 M at an organic phase HNO_3 concentration of 0.4 M.[50] Although the Ln^{3+} ions are poorly extracted by TBP, both Ce^{4+} and UO_2^{2+} are well extracted and reduction of any Ce^{IV} present to Ce^{III} is necessary prior to processing. TBP extracts Th^{4+} hardly at all from H_2SO_4 solutions, D_{Th} being less than 0.1 for 30 v/o TBP/benzene over the 0.5–9 M H_2SO_4 concentration range.[144]

The separation of Th^{4+} from the lanthanides may be achieved using 50–70 v/o TBP/OK as extractant against an aqueous phase 5 M in nitric acid.[232] This will then extract the Th^{4+} but, provided the organic phase is near saturation with Th^{4+}, not the Ln^{3+} ions. Sulfate or phosphate must not be present in the process solutions since they suppress Th^{4+} extraction. A typical thorium purification process[50] might involve the dissolution of the ore concentrate in nitric acid to give a solution containing *ca.* 170 g dm^{-3} Th^{4+} in 4 M HNO_3. This is contacted with 5 v/o TBP/xylene to extract UO_2^{2+} and give an aqueous stream containing *ca.* 135 g dm^{-3} Th^{4+} in 3.5 M HNO_3. This is next contacted with 40 v/o TBP/xylene to extract Th^{4+}, leaving the Ln^{3+} ions in the aqueous phase. The organic phase is washed with 2 M $NaNO_3$ in 0.1 M HNO_3 to complete the Ln^{3+} removal before the Th^{4+} is back extracted with 0.02 M HNO_3 to give a purified aqueous $Th(NO_3)_4$ solution and a barren organic phase for recycle. The thorium may subsequently be precipitated with oxalate and calcined to give a solid ThO_2 product containing less than 0.07 p.p.m. uranium, 0.63 p.p.m. cadmium, 60 p.p.m. silicon and less than 0.05 p.p.m. boron.

65.2.3.3 Thermal reactor fuel preparation

Uranium tetrafluoride is a key intermediate in the production of thermal reactor fuels. It may be prepared directly from uranyl solutions by reduction of the U^{VI} to U^{IV} and addition of HF to precipitate UF_4. A number of processes have been developed to produce UF_4 by this wet route,[68] which may be used to produce UF_4 at the ore processing site. These employ iron, SO_2/Cu^{2+} or electrolysis for the reduction step, the latter being preferred since it introduces no contaminants into the solution. The reduction of U^{VI} in various media has been studied to assess the effect of complexation on the reduction reaction.[233] The standard potential for the reduction of UO_2^{2+} to U^{4+} in 1 M $HClO_4$ has been given as +0.32 V.[234] The overall formation constants of U^{4+} fluoride complexes in 1 M NaCl were found[235] to be $\log \beta_2 = 13.12$, $\log \beta_3 = 17.46$ and $\log \beta_4 = 21.8$. Although wet processes have been developed as a 'short cut' to UF_4, the most widely used process at present involves dry processing.

In the dry process,[2,11,50,51,236,237] uranyl nitrate from the purification process is thermally denitrated to give UO_3, which is then reduced to UO_2 as shown in equations (116) and (117). Differential thermal analysis studies suggest[238] that N_2O_5 is the initial gaseous reaction product, but this then decomposes or reacts with moisture. The UO_2 is next hydrofluorinated according to equation (118) and the product may either be converted to uranium metal for use in Magnox reactors by reduction with Ca or Mg, or it may be converted to UF_6 for enrichment prior to use in AGR, PWR or other reactor types requiring enriched uranium fuel. UF_6 is a volatile solid having a heat of sublimation of 48.1 kJ mol^{-1} at 64 °C and is produced by fluoridation according to equation (119). The volatility of UF_6 allows isotope separation processes which require gaseous materials to be used. The gaseous diffusion process is now being superseded by centrifugal isotope separations in the gas centrifuge system, which is less energy intensive.[237] Laser isotope separation is also under investigation, though far from commercial application, and $U(OMe)_6$ has been found to give an enrichment factor of up to 1.0315 in a single irradiation test, an order of magnitude better than a single diffusion stage.[239] Uranium enriched to 3% ^{235}U has been prepared by a redox chromatography method based on equation (120), which has an equilibrium constant of 1.0013.[240] Kinetic isotope effects in continuous solvent extraction cycles may also effect isotope separations, as may ion exchange processes. The separation of uranium isotopes by such chemical methods has been reviewed,[241] but at present only the processes based on UF_6 are in commercial use.

$$UO_2(NO_3)_2{\cdot}6H_2O \rightarrow UO_3 + NO + NO_2 + O_2 + 6H_2O \quad (116)$$

$$UO_{3(s)} + H_{2(g)} \xrightarrow{480°C} UO_{2(s)} + H_2O_{(g)} \qquad \Delta H° = -46.6 \text{ kJ mol}^{-1} \quad (117)$$

$$UO_{2(s)} + 4HF_{(g)} \xrightarrow{450°C} UF_{4(s)} + 2H_2O_{(g)} \qquad \Delta H° = -78.1 \text{ kJ mol}^{-1} \quad (118)$$

$$UF_{4(s)} + F_{2(g)} \xrightarrow{450°C} UF_{6(g)} \qquad \Delta H° = -110{\cdot}4 \text{ kJ mol}^{-1} \quad (119)$$

$$^{238}U^{VI} + ^{235}U^{IV} \rightleftharpoons ^{235}U^{VI} + ^{238}U^{IV} \quad (120)$$

After enrichment the UF_6 must be converted to UO_2 powder for fuel fabrication. This may be achieved by hydrolysis to UO_2F_2 and treatment with ammonia in water to give ammonium diuranate, or by treatment with NH_3 and CO_2 to give uranyl carbonate according to equation (121). The ammonium diuranate may be calcined to U_3O_8, which is reduced to UO_2 with hydrogen. The carbonate complex may be decomposed with hydroxide before calcining. A recently developed dry route to UO_2 is now used by British Nuclear Fuels Ltd (BNFL) in the UK. This integrated dry route[11] involves the direct hydrolysis and reduction of UF_6 as shown in equation (122). The oxide produced may be pressed into pellets and loaded into stainless steel cans for use in AGR or zirconium alloy cans for use in PWR.

$$UF_6 + 5H_2O + 10NH_3 + 3CO_2 \rightarrow (NH_4)_4[UO_2(CO_3)_3] + 6NH_4F \quad (121)$$

$$UF_6 + 2H_2O + H_2 \xrightarrow{600°C} UO_2 + 6HF \quad (122)$$

65.2.3.4 Fast reactor fuel preparation

The preparation of fuel for the plutonium LMFBR requires the conversion of the plutonium nitrate product from fuel reprocessing to PuO_2. This may be achieved by precipitation of Pu^{IV} hydroxide and calcining or by precipitation of $Pu(C_2O_4)_2$, which has a formation constant of log $\beta_2 = 16.9$,[242] followed by calcining. Mixed PuO_2/UO_2 or ThO_2/UO_2 fuel may be prepared by mixing the powdered oxides or by coprecipitation from mixed solutions and calcining. However, the handling of fine powders presents special safety problems when dealing with the highly radiotoxic plutonium or ^{235}U oxides. In order to avoid the need for handling powders the 'Sol-Gel' or 'Gel Precipitation' process has been developed.[14,243] In this approach the concentrated actinide nitrate solutions from fuel reprocessing are blended to give the required U : Pu or U : Th ratio. An organic polymer is then added to act as a gelling agent along with a modifier to complex the metal and prevent premature reaction with the gelling agent. The prepared solution is then passed through a vibrating orifice which produces droplets of uniform size. These fall through a column of concentrated ammonia solution and are converted to a spherical hydrous oxide gel. The nature of the gel is complex and it probably contains polymeric species with μ-oxo bridges between Pu^{4+} or Th^{4+} ions. The uranium appears to precipitate as ammonium diuranate crystallites but plutonium and thorium form amorphous hydrous oxides. The gel spheres are next washed with

water, dried under controlled conditions and 'debonded' by heating in CO_2 to remove the organic material. The debonded spheres are then sintered at 1450 °C in argon containing 5% H_2 to give the finished oxide spheres. These are hard and dust free and may be prepared conveniently in a range of sizes, 80×10^{-6} and 800×10^{-6} m being routinely prepared in a UK pilot plant. These spheres may then be pressed into larger fuel pellets without the need for oxide powder formation at any stage in the process. The pellets are packed into stainless steel cans for irradiation. Carbide and nitride fuels have also been investigated as alternatives to oxides and the High Temperature Reactor has utilized graphite coated UC_2 or $(U,Th)C_2$ spheres.[244] However, these systems are not yet utilized in commercial power generation.

65.2.4 Reprocessing of Irradiated Fuels

After irradiation in the reactor the fuel is discharged and placed in cooled storage for several months. During this time the shorter half-life fission products, such as ^{131}I, decay and the heat output of the spent fuel declines.[13] The cooled fuel may then be dispatched for long-term storage or for reprocessing. The first step in the reprocessing operation will be to remove the fuel from the container which separated it from the primary reactor coolant. This 'decanning' or 'dejacketing' operation is usually performed mechanically, but chemical methods have also been used. The exposed fuel is then dissolved and separated from insoluble materials before processing to separate the FPs and other actinides from the uranium. The separation processes used today involve solvent extraction as the primary method, but in the past the precipitation of Pu^{IV} within a $BiPO_4$ matrix has been used as an actinide separation method. Anion exchange based on the formation of $[Pu(NO_3)_6]^{2-}$ in concentrated nitric acid solutions has also been investigated and utilized for plutonium purification. However, the dangers of exothermic reactions between the resin and nitric acid led to this method being discontinued.

Table 10 Some Decontamination Factors Required of Fuel Reprocessing

	Required decontamination factors for process product streams							
		Present BNFL process[b]			*THORP*[a]	*PFR plant*[b]		
Element	*Magnox*[a] *Uranium*	*Uranium*	*Plutonium*	*HLW*	*Uranium*	*Uranium*	*Plutonium*	*HLW*
Total FP	—	5×10^6	5×10^7	—	—	5×10^7	10^7	—
Ru	10^6	—	—	—	10^8	—	—	—
Tc	1.0	—	—	—	10^3	—	—	—
U	—	—	10^7	2×10^4	—	—	10^5	$>2\times10^4$
Np	1.0	—	—	—	5×10^4	—	—	—
Pu	10^5	2×10^6	—	2×10^3	5×10^8	5×10^7	—	$>2\times10^4$

[a] From ref. 11; THORP = Thermal Oxide Reprocessing Plant.
[b] From ref. 245; PFR = Prototype Fast Reactor at Dounreay, UK; HLW = High Level Waste in which the bulk of the fission products (FP) are concentrated.

Several exacting requirements are placed on the solvent extraction process. Firstly, it must achieve essentially quantitative recovery of uranium and plutonium or thorium. Secondly, it must achieve acceptable actinide and FP decontamination factors for the product streams. Increasingly stringent control of waste discharges, and higher fuel irradiation in modern thermal and fast reactors, are making even greater demands[245] on processes, as indicated in Table 10. Thirdly, the process must endeavour to concentrate the radioactive wastes in a single stream suitable for treatment and long-term storage. Further constraints arise from the need to shield operators from the radiation emitted by the radioactive components, to contain the highly radiotoxic materials involved and to exclude the possibility of a critical assembly of fissile material. Thus the plant must not only meet extremely high standards of containment but most of the operations must be carried out remotely, behind thick concrete walls to provide a biological shield. The problem of criticality can arise with quite dilute solutions of fissile material. A solution containing 0.5–1.0 kg of fissile material at a concentration of *ca.* 10 g dm^{-3} may become critical if the correct geometry is achieved.[246] This would result in an intense burst of radiation which might endanger plant operators. It would also produce highly radioactive FPs and cause rapid heating of the process solutions, with the risk that control and containment of the process may be lost. Although the operating conditions of a process would be devised to avoid criticality, this does not guarantee

that it will not arise through operator error or equipment malfunction. It is thus necessary to take positive steps to prevent criticality. One approach is to add a strong neutron absorber such as boric acid or gadolinium nitrate. However, this adds extra material to the process streams and subsequent decontamination of the product may be difficult. A far better approach is to design the plant construction to give geometric safety. Thus under no conditions could criticality occur if the plant dimensions are suitably chosen. The minimum diameter of an infinite cylinder of a fissile material in solution which cannot become critical is *ca.* 11 cm. Similarly, an infinite slab less than 4.3 cm thick will not allow criticality with ^{239}Pu solutions, although this figure falls to 1.4 cm for ^{233}U.[245] The use of cylindrical reaction vessels of limited diameter and of slab tanks of limited thickness, separated as necessary by neutron absorbing materials, thus provides a structural guarantee that criticality will not occur.

The need for shielding, containment and the geometric prevention of criticality during fuel reprocessing has a bearing on the choice of equipment and process used. Solvent extraction is well suited to remote operation with minimal maintenance requirements and involves only the transfer of liquids, which greatly simplifies the movement of materials through the plant. The main stages of the solvent extraction process are summarized in Figure 29. Both the Purex process, currently used for U–Pu separation, and the Thorex process, used for U–Th separation, have these features in common, but differ substantially in detail and in the manner in which actinide partition is effected. There are also differences in the Purex process used for thermal reactor fuels and for plutonium breeder LMFBR fuels. Thermal reactor fuel will contain *ca.* 95% uranium and

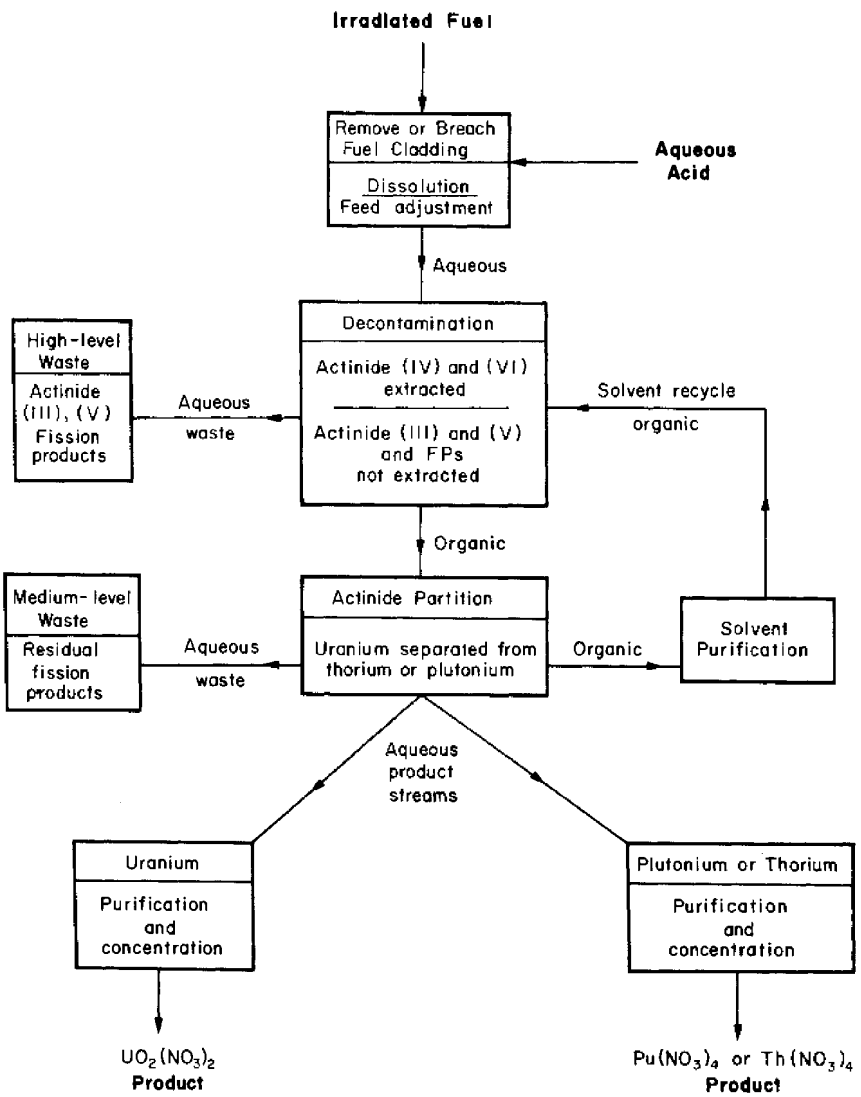


Figure 29 An outline process for irradiated fuel reprocessing by solvent extraction

ca. 1% other actinides[13] so that the other actinides do not have a major affect on uranium behaviour during extraction. However, LMFBR fuel may contain *ca.* 20% plutonium, which will have a significant affect on uranium extraction and *vice versa.* The treatment of breeder reactor fuels will thus be given separate consideration.

65.2.4.1 Fuel decanning and dissolution

The cladding used to prevent contact between nuclear fuel and the primary coolant in power reactors is currently one of three materials. The PWR and CANDU reactors use fuel clad in Zircaloy, a zirconium alloy, AGR and LMFBR reactors use stainless steel and the Magnox reactors use a magnesium alloy. Graphite coated spheres of UO_2/ThO_2 are used in the High Temperature Gas Cooled Reactor (HTR). Aluminum clad uranium metal has also been used in some research reactors and, in this case, both the fuel and cladding could be dissolved in nitric acid. In the case of Zircaloy, chemical dissolution is possible using ammonium fluoride according to equation (123). In the absence of nitrate the reaction is slow and produces substantial amounts of hydrogen.[247] Magnox can be dissolved in formic acid and stainless steel in *aqua regia.* However, the chemical decladding approach introduces large quantities of nonradioactive contaminants into the process wastes, increases the metal inventory of the plant and makes effective actinide decontamination more difficult. Consequently, mechanical decanning processes are preferred for cladding removal.[13] At BNFL, Magnox is 'peeled' from the uranium metal and separated before fuel dissolution. In the cases of Zircaloy clad PWR fuel, and stainless steel clad AGR and LMFBR fuel, a 'chop-leach' process is used. The fuel elements are cut into short sections and then sent to the dissolver. There the fuel is leached out using nitric acid and the empty cladding sections or 'hulls' are then separated for storage as solid radioactive waste.

$$2Zr + 9NH_4^+ + 12F^- + NO_3^- \rightarrow 2ZrF_6^{2-} + 10NH_3 + 3H_2O \quad (123)$$

The dissolution of thermal reactor fuel, with its high uranium content, is readily achieved using concentrated nitric acid. Dissolution of uranium metal in 11.7 M HNO_3 proceeds according to equation (124) or, if taken to final acid concentrations of a few tenths molar, equation (125).[13] The process is exothermic, the heat of reaction being $-1024\ kJ\ mol^{-1}$ for equation (126). In contrast, the dissolution of UO_2 according to equation (127) is endothermic to the extent of $0.1\ kJ\ mol^{-1}$. Thus cooling is required during metal dissolution in Magnox fuel reprocessing, but heating is needed during the dissolution of oxide fuels.[11] The bulk of the metallic fission products present dissolve as oxidation state (I), (II) or (III) nitrates, depending upon the element. However, in oxide fuels some 0.1–0.3% of the total may remain in the form of undissolved particles or 'fission product insolubles' containing an alloy of Ru, Rh, Mo, Te, Zr and Pd. The actinides dissolve as UO_2^{2+}, Pu^{4+} and PuO_2^{2+}, Am^{3+} and Cm^{3+}. In the case of neptunium, NpO_2^{2+} forms at high HNO_3 and low HNO_2 concentrations but, at low acidities, NpO_2^+ and Np^{4+} will also be present.

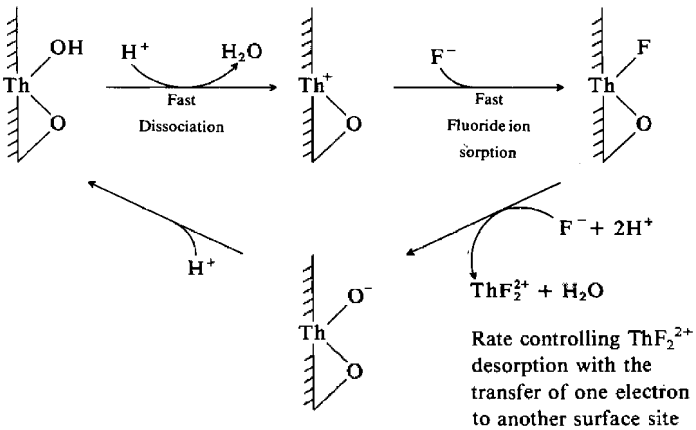
$$U + 4.5HNO_3 \rightarrow UO_2(NO_3)_2 + 1.57NO + 0.84NO_2 + 0.0005N_2O + 0.043N_2 + 2.25H_2O \quad (124)$$

$$U + 5.5HNO_3 \rightarrow UO_2(NO_3)_2 + 1.25NO + 2.25NO_2 + 2.75H_2O \quad (125)$$

$$U + 4HNO_3 \rightarrow UO_2(NO_3)_2 + 2NO + 2H_2O \quad (126)$$

$$3UO_2 + 8HNO_3 \rightarrow 3UO_2(NO_3)_2 + 2NO + 4H_2O \quad (127)$$

The dissolution of breeder reactor fuels presents a more difficult problem because of the insoluble nature of PuO_2 and ThO_2. Difficulty in dissolving LMFBR fuels is likely to arise when the PuO_2 content approaches or exceeds *ca.* 30%. The dissolution of PuO_2 has been reviewed by Ryan and Brag,[248] who point out that PuO_2 is insoluble at nitric acid concentrations below 5 M on thermodynamic grounds. The method of preparation of oxide fuels may affect their dissolution behaviour. A study of this phenomenon[249] has revealed a correlation between the exchange capacity of the oxide and its dissolution rate in 7.5 M nitric acid. Dissolution may be promoted by oxidants such as Ce^{IV} but reactions with FPs, especially ruthenium, can interfere with this action. An alternative approach is to add F^- to the nitric acid to promote dissolution. The mechanism of dissolution of ThO_2 and PuO_2 by HNO_3/HF mixtures has been investigated[250–252] and is probably similar in both cases. ThO_2 is more readily dissolved than PuO_2 but higher fabrication temperatures decrease ThO_2 fuel solubility. To obtain meaningful mechanistic data, experimental conditions



Scheme 5

in which dissolved F^- is not extensively complexed by liberated Th^{4+} are required. The dissolution mechanism proposed on the basis of data obtained under these conditions is illustrated in Scheme 5. This involves hydration of the ThO_2 surface followed by the replacement of OH^- by F^-. This species then adsorbs HNO_3 with an activation enthalpy of 44 kJ mol^{-1} as the rate determining step prior to dissolution. The addition of 0.05 M HF to 12 M HNO_3 leads to a substantial increase in dissolution rate.[252] The effect of metallic impurities on the rate of PuO_2 dissolution by HNO_3/HF has also been investigated and metal ions forming strong fluoride complexes greatly reduced the dissolution rate.[253] The dissolution of ThO_2 from Zircaloy cladding by 0.02–0.04 M HF in 8–12 M HNO_3 has also been reported.[254] The addition of F^- to dissolver solutions poses problems in terms of the corrosion of stainless steel plant components; F^- complexing may also interfere with the chemistry of subsequent solvent extraction processes. The corrosion of steel may be reduced by complexation of the F^- with Zr^{4+} or Al^{3+}, but a dissolution process based on oxidant addition may be preferred. In studies[255,256] of irradiated LMFBR fuel dissolution by HNO_3 it appeared that at least 1–3% of the Pu would remain as insoluble dissolver residues in the absence of F^-. The possibility of using a secondary, small scale, dissolution stage involving F^- to dissolve these residues has been suggested.[256]

Uranium and plutonium carbide fuels have also been investigated and their dissolution in nitric acid results in the formation of organic acids as well as CO_2.[257,258] In the case of $(U_{0.8}Pu_{0.2})C$ fuel, which has better thermal conductivity than the mixed oxides, dissolution in 2–14.4 M nitric acid at 30–80 °C gave only UO_2^{2+} and Pu^{4+} in solution. Between 32% and 62% of the carbide carbon was converted to CO_2.[258] However, the organic acids formed, particularly oxalic and mellitic acids, may have a detrimental effect on subsequent solvent extraction processes. An investigation of this problem indicated that the benzenepolycarboxylic acids were insufficiently soluble to give significant actinide complexation. However, this was not the case for oxalic acid. In media 4 M in NO_3^- the stability constants for oxalate complexation were found to be $\log \beta_1 = 6.28 \pm 0.11$ for $UO_2(C_2O_4)$ formation, $\log \beta_1 = 8.30 \pm 0.07$ for $Pu(C_2O_4)^{2+}$ formation and $\log \beta_2 = 14.9 \pm 0.3$ for $Pu(C_2O_4)_2$ formation. It was concluded that, in the Purex process, oxalate complexation of Pu^{4+} was likely to result in substantial proportions of plutonium being rendered inextractable. However, in the case of uranyl ions, less than 5% would be rendered inextractable.

65.2.4.2 Solvent extraction fundamentals

Numerous researchers have contributed to the fundamental understanding of solvent extraction equilibria and their work has been reviewed in several texts which are relevant to the application of solvent extraction in the nuclear industry.[4,5,90,260] A generalized account of the topic has been provided[4] based on work by Irving *et al.* The distribution of a metal between an aqueous and an organic phase may be defined by a distribution coefficient, D_M, given by equation (38) for the specific case of $M = U^{VI}$. This coefficient includes all metal containing species in the aqueous and organic phases. If a single metal complex only is considered the overall stoichiometric formation constant, β_{hmlws}, for the completely general complex $[H_hM_mL_l(H_2O)_wS_s]$, where L is an anionic ligand, S a neutral solvating ligand, M is the metal ion in question and charges are omitted for simplicity, is given by equation (128). The partition coefficient, P_{hmlws}, for this specific complex

is given by equation (129). The coefficients β_{hmlws} and P_{hmlws} will only be genuine constants if the aqueous and organic phase activity coefficients remain constant. This assumption will introduce uncertainties in the interpretation of results based on concentration data alone. However, because

$$\beta_{hmlws} = [H_hM_mL_l(H_2O)_wS_s]/[H]^h[M]^m[L]^l[H_2O]^w[S]^s \tag{128}$$

$$P_{hmlws} = [H_hM_mL_l(H_2O)_wS_s]_{(org)}/[H_hM_mL_l(H_2O)_wS_s]_{(aq)} \tag{129}$$

of the difficulty in measuring activities, many studies of solvent extraction as a metal separation process must assume constant or unit activity coefficients. Some control of activity coefficients in the aqueous phase is possible by using constant high ionic strength conditions. In the non-aqueous phase, activity coefficient variations may be small if uncharged complexes are involved. However, where ion pairs are extracted the coefficients may become very sensitive to metal ion concentration. Substantial changes in ligand concentrations during extraction may have a marked effect on activity coefficients for both phases. Continuing with the simplifying assumption of constant activity coefficients and using concentrations alone, the distribution coefficient, D_M, is given by summing all aqueous and organic phase complexes as shown in equation (130), which may be rewritten as (131) by substituting from equations (128) and (129). This equation may be simplified by deleting terms for which $P_{hmlws} = 0$, by omitting charged species which are presumed not to extract and by the use of charge and mass balance considerations. In the example of metal extraction by a solvating extractant such as TBP the extraction reaction is given by equation (132), where $h = 0$ and the extractant is hydrated by x water molecules. In this case the single extracted complex is monometallic and unprotonated so that partial differentiation of the logarithmic form of equation (131) with respect to the extractant concentration gives equation (133) where $\bar{s}_{(org)}$ and $\bar{s}_{(aq)}$ are the average solvation numbers for M with S in the organic and aqueous phases respectively. Normally $\bar{s}_{(aq)} = 0$, since the solvated complex is present only in the organic phase. Thus, provided other parameters are held constant, a plot of log D_M against log $[s]$ should yield a line of slope $\bar{s}_{(org)}$, giving the average reaction stoichiometry with respect to s. Similar approaches may be used to determine the stoichiometry with respect to other reactants.

$$D_M = \sum m[H_hM_mL_l(H_2O)_wS_s]_{(org)}/\sum m[H_hM_mL_l(H_2O)_wS_s]_{(aq)} \tag{130}$$

$$D_M = \frac{\sum P_{hmlws}\beta_{hmlws}m[H]^h[M]^m[L]^l[H_2O]^w[S]^s}{\sum \beta_{hmlws}m[H]^h[M]^m[L]^l[H_2O]^w[S]^s} \tag{131}$$

$$M^{l+} + lL^- + (w - sx)H_2O + sS(H_2O)_x \rightleftharpoons ML_l(H_2O)_wS_s \tag{132}$$

$$(\delta \log D_M/\delta \log [S])_{[M][L][H_2O]} = \bar{s}_{(org)} - \bar{s}_{(aq)} \tag{133}$$

In the case of anionic chelating extractants such as HDEHP, HDBP, HTTA or generally HA, the reaction stoichiometry with respect to the metal, M^{z+}, and extractant, HA, is given by equation (134). In this case, D_M is given by equation (135),[90] where $[MA_x]$ is the neutral extracted species and $[MA_n]$ represents all the aqueous phase species for $n = 0$–N of which MA_x is one. A plot

$$M^{z+}_{(aq)} + nHA_{(org)} \rightleftharpoons MA_{n(org)} + nH^+ \tag{134}$$

$$D_M = P_x\beta_x[A]^x \Big/ \sum_0^N \beta_n[A]^n \tag{135}$$

of log D_M against log $[A^-]$ will give a line of slope x at small $[A^-]$ values where $\beta_0 = 1$ in the denominator and M^{z+} is the dominant aqueous phase species. At high $[A^-]$ values the slope becomes $x - N$, a straight line plot indicating that the complex has become coordinatively saturated. If a single complex MA_n dominates both the organic and aqueous phases then D_M becomes independent of $[A^-]$ and equal to P_n. In the case where a neutral ligand S is also involved the reaction stoichiometry is given by equation (136). In the extraction of actinides by reagents such as HDEHP or HDBP, S may be HA or a synergist such as TBP or TOPO. Equation (137) now defines D_M where MA_xS_y is the neutral extracted species among the range of aqueous phase complexes MA_nS_p for $n = p = 0$ to $n = N$ and $p = P$. Partial differentiation of the logarithmic form

$$M^{z+}_{(aq)} + nHA_{(org)} + pS_{(org)} \rightleftharpoons MA_nS_{p(org)} + nH^+_{(aq)} \tag{136}$$

$$D_M = \sum P_{xy}\beta_{xy}[A]^x[S]^y \Big/ \sum_0^N \sum_0^P \beta_{np}[A]^n[S]^p \tag{137}$$

of (137), holding [A] or [S] constant, leads respectively to equations (138) and (139), where $\bar{p}$ and $\bar{n}$ are the mean number of S and A^- ligands bound to the metal in the aqueous phase. A plot of log D_M against log [S] at constant $[A^-]$ thus gives a line whose slope corresponds with the difference between the number of ligands S bound in the organic and aqueous phases. As [S] tends to 0 the slope tends to y. Similarly, x may be determined graphically.

$$(\delta \log D_M/\delta \log [S])_{[A]} = y - \bar{p} \tag{138}$$

$$(\delta \log D_M/\delta \log [A])_{[S]} = x - \bar{n} \tag{139}$$

In the case of the extraction of anionic complexes by alkylammonium reagents according to equation (140), D_M is given[90] by equation (141) in which ML_x^{p-} is the only extracted species and various ML_n^{z-n} complexes are present in the aqueous phase; K_{DM} is the equilibrium constant for reaction (140). Equation (141) indicates that, as $[L^-]$ increases from 0, a greater proportion of M^{z+} will be in the form of ML_x^{p-} so that D_M should increase. However, provided x is less than the maximum value of n in the aqueous phase, *i.e.* $x < N$, at very high $[L^-]$ the concentration of ML_x^{p-} will begin to fall as ML_n^{z-n}, where $x < n$, become the dominant species. Thus a plot of D_M against aqueous phase acidity will reach a maximum when $p + z = x$ and then D_M will fall off with increasing HL, as shown in Figure 11. Partial differentiation of the logarithmic form of equation (141) gives equation (142), showing that a plot of log D_M against $\log [R_3NH^+L^-]_{(org)}$ should have a slope of p, indicating the charge on the extracted species and thus the number of amines per extracted complex. Application of this procedure is complicated by the need to know $[R_3NH^+L^-]_{(org)}$, which represents only one of a number of amine species present in the organic phase. A very carefully controlled set of conditions where $[R_3N] \ll [R_3NH^+L^-]$, no acid is extracted, no association of amine species occurs and trace metal concentrations are present, is needed for these total concentrations of R_3N in the organic phase to be a valid measure of $[R_3NH^+L^-]_{(org)}$.

$$pR_3NH^+L^-_{(org)} + ML_n^{p-}{}_{(aq)} \rightleftharpoons (R_3NH^+)_pML_n^{p-}{}_{(org)} + pL^-_{(aq)} \tag{140}$$

$$D_M = \frac{K_{DM}[R_3NH^+L^-]^p_{org}\beta_x[L^-]^{x-p}}{\sum_0^N \beta_n[L^-]^n} \tag{141}$$

$$\delta \log D_M/\delta \log [R_3NH^+L^-]_{(org)} = p \tag{142}$$

This brief outline serves to illustrate the ways in which the stoichiometries of extraction reactions may be determined experimentally. A full account of extraction equilibria and their use in measuring stability constants for actinide complexation, as well as reaction stoichiometries, is given by Ahrland *et al.*[90]

Once the partition behaviour of a solute, M, in a mixed phase system has been defined it is possible to predict the outcome of simple batch extraction experiments. After a single equilibration of a volume, V_a, of an aqueous phase containing a solute M with a volume, V_o, of an organic extractant, the mass distribution ratio of M between the organic and aqueous phases is given by the extraction factor, E_f, in equation (143). (This value is often expressed as a percentage extraction factor, E, where $E = E_f \times 100\%$.) A single-stage batch extraction experiment is represented schematically in Figure 30a, where x_0 and x_1 are respectively the concentrations of M in the aqueous feed solution and raffinate, and y_p and y_0 are respectively the concentrations of M in the organic product and feed solution. In this case $y_0 = 0$ and $V_a x_0$ is the total mass of M present. A mass balance consideration of this process gives equation (144). The mass fraction, $W_{o,1}$, of the total M present which is extracted into the organic phase is given by equation (145) while the mass fraction, $W_{a,1}$, remaining unextracted in the aqueous phase is given by equation (146). When the aqueous phase is successively contacted by n batches of fresh solvent in a cross-current multistage process, as illustrated in Figure 30b, the fraction, $W_{a,n}$ of M remaining in the aqueous

$$E_f = \frac{V_o}{V_a} D_M \tag{143}$$

$$V_a x_0 = V_a x_1 + V_o y_p \tag{144}$$

$$\text{Fraction extracted} = \frac{V_o y_p}{V_a x_0} = \frac{E_f}{(1+E_f)} = W_{o,1} \tag{145}$$

$$\text{Fraction unextracted} = \frac{V_a x_1}{V_a x_0} = \frac{1}{(1+E_f)} = W_{a,1} \tag{146}$$

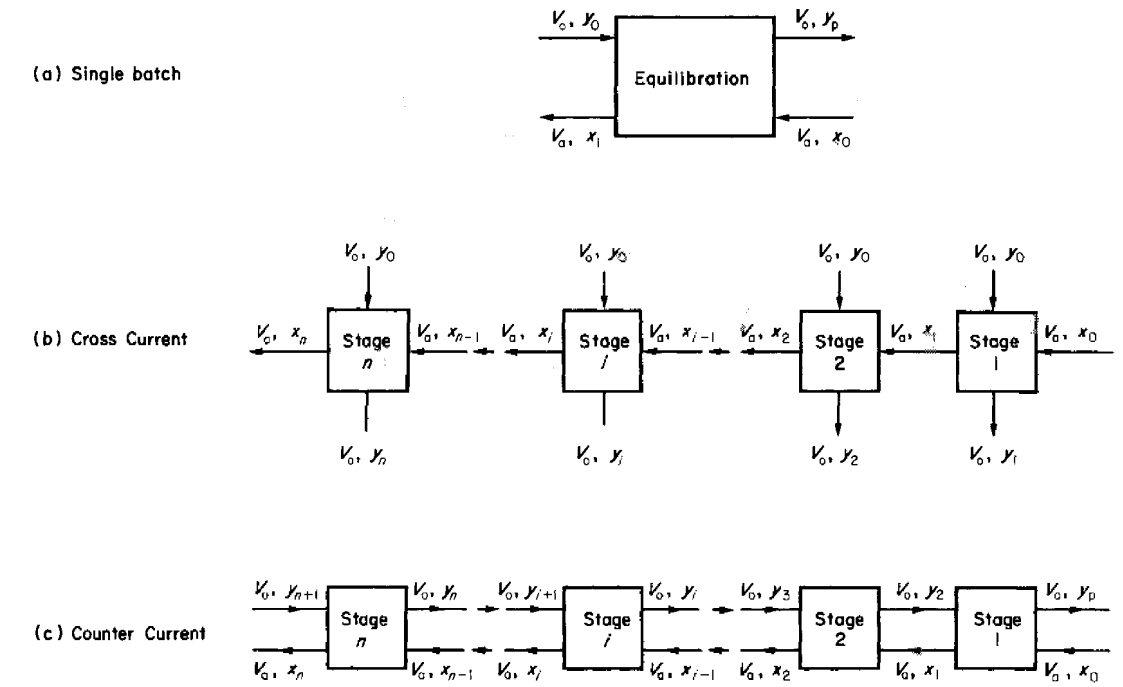


Figure 30 Types of solvent extraction strategy in which V_o is the organic phase volume flowrate, y_o the concentration of solute in the organic feed, y_p the concentration of solute in the organic product and y_i the concentration in the organic phase leaving stage i. Corresponding values for the aqueous phase are denoted by V_a, x_o, x_p and x_i respectively

phase after the nth extraction is given by equation (147).[262] Assuming a D_M value of 1 a single batch extraction with $V_a = V_o$ would have $E_f = 1$ and would give $W_{a,1} = W_{o,1} = 0.5$. In contrast, splitting the extractant into five equal batches, so that $n = 5$ and $V_a = 5V_o$ for each stage, we have $E_f = 0.2$, $W_{a,5} = 1.2^{-5} = 0.40$ so that the combined organic phases have $W_o = 0.6$. This approach thus offers some improvement in solute recovery but is generally inefficient because the extractive capacity of the unloaded solvent is not being fully utilized in the later stages of contact with the more dilute aqueous phase.

$$\frac{x_n}{x_0} = \frac{1}{(1+E_f)^n} = W_{a,n} \quad \text{(cross-current)} \tag{147}$$

Far better use is made of the solvent's extraction capacity in a counter-current multistage process such as that illustrated in Figure 30c. In this process the loaded solvent product is contacted with the highest aqueous phase concentration of solute, x_0, just prior to removal. This then maximizes the organic phase solute concentration y_p. The mass balance for stage i is given by equation (148) and for the final stage by equation (149), where $y_{n+1} = 0$ at stage n. In this case, $W_{a,n}$ is given by equation (150), which reduces to $W_{a,n} = 1/(1+n)$ when $E_f = 1$. Thus in the case described above, five counter-current stages with $V_a = V_o$ and $D_M = 1$ give $W_{a,5} = 0.17$ and thus $W_{o,5} = 1 - W_{a,5} = 0.83$, a considerable improvement in the proportion of M transferred to the organic phase.

$$V_a x_{i-1} + V_o y_{i+1} = V_a x_i + V_o y_i \tag{148}$$

$$V_a x_{n-1} = V_a x_n + V_o y_n \tag{149}$$

$$\frac{x_n}{x_0} = \frac{E_f - 1}{E_f^{n+1} - 1} = W_{a,n} \quad \text{(counter-current)} \tag{150}$$

In order to illustrate how these three processes might perform in practice we may consider a hypothetical example. An aqueous solution containing equal mass concentrations of an actinide, An, and a lanthanide fission product, Ln, are to be separated using an organic extractant for which $D_{An} = 10$ and $D_{Ln} = 0.1$. Using a phase volume ratio $V_o/V_a = 1$ we have E_f values of 10 for An and 0.1 for Ln. A single batch extraction would then give $W_{o,1}$ values of 0.91 for An and 0.091 for Ln. This corresponds with a decontamination factor, DF_{Ln}, of 10 for the removal of Ln from An in the organic phase product. A five-stage cross-current separation would give $W_{o,5}$ values of

0.999994 for An and 0.38 for Ln, corresponding with a DF_{Ln} of 2.6. Finally, a five-stage counter-current separation would give $W_{o,5}$ values of 0.999991 for An and 0.10 for Ln with a corresponding DF_{Ln} of 10. These results show that, compared with a single batch extraction, the cross-current process offers an improved An recovery at the expense of a reduced DF_{Ln}. However, a high An recovery is also possible using the counter-current process without the penalty of a reduced DF_{Ln} value. The counter-current process thus offers advantages when the dual objectives of high actinide recovery and good fission product decontamination are considered.

Despite the success of the counter-current process in comparison with single batch or cross-current processes, a DF_{Ln} value of 10 is modest in view of the hundredfold difference between D_{An} and D_{Ln}. Better decontamination can be achieved if a washing or scrub section is incorporated in the process. This involves contacting the loaded organic product stream with an aqueous phase having a low or zero Ln concentration. The raffinate from this section is then combined with the aqueous feed to the extraction section, as illustrated in Figure 31. The mass fraction, $W_{a,n+m}$, of a solute remaining in the aqueous phase after n stages of extraction and m stages of scrubbing with $x_0 = 0$ in such a process is given[90] by equation (151), where $E_{f(ex)}$ is the extraction factor for the extract section and $E_{f(sc)}$ is the extraction factor for the scrub section. This reduces to $W_{a,n+m} = (E_f^m - 1)/(E_f^{m+n} - 1)$ when $E_{f(ex)} = E_{f(sc)} = E_f$. Applying such a process to the example of An and Ln might involve three extraction and two scrub stages with $V_o/V_a = 1$ in the extract section and $V_o/V_a = 2$ in the scrub section. Assuming no change in distribution coefficients, this then gives $E_{f(ex)}$ values of 10 for An and 0.1 for Ln and $E_{f(sc)}$ values of 20 for An and 0.2 for Ln.

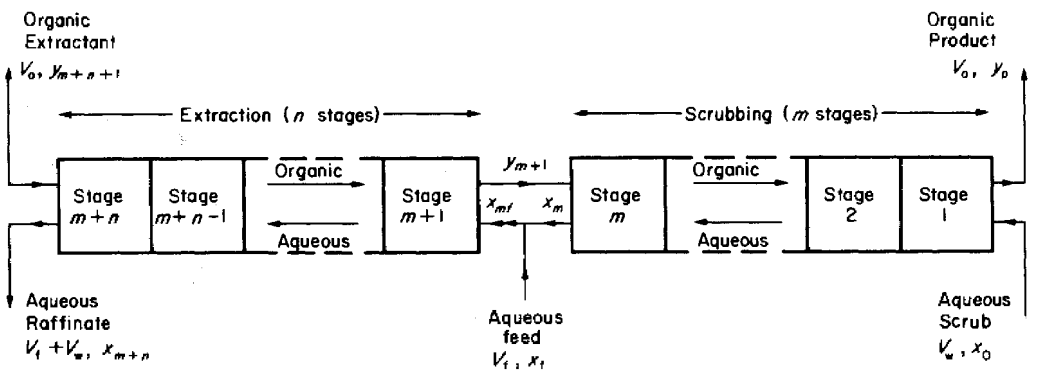


Figure 31 A counter-current solvent extraction contacter incorporating n stages of extraction and m scrub stages. V_o, V_f and V_w are the volume flow rates of the organic feed, aqueous feed and aqueous scrub respectively. The concentration of solute in the organic feed product and after stage m are given by y_o, y_p and y_m. Corresponding values for the aqueous phase are denoted by x_o, x_p and x_m respectively

Using equation (151), $W_{o,5}$ values of 0.99906 for An and 0.0182 for Ln are obtained, giving a DF_{Ln} of 55. This modification of the counter-current process thus offers a substantial increase in DF_{Ln} at the expense of a small reduction in An recovery.

$$W_{a,n+m} = \frac{(E_{f(ex)} - 1)(E_{f(sc)}^m - 1)}{(E_{f(ex)}^{n+1} - 1)(E_{f(sc)} - 1)E_{f(sc)}^{m-1} + (E_{f(sc)}^{m-1} - 1)(E_{f(ex)} - 1)} \quad (151)$$

The example of An and Ln given above is somewhat artificial since, in practice, conditions would be chosen to keep D_{FP} well below 0.1 while $D_{An^{IV}}$ or $D_{An^{VI}}$ might be greater than 10. However, the figures do illustrate how multistage counter-current extraction processes can achieve high actinide recovery as well as high fission product decontamination. The process requirements for nuclear fuel reprocessing can often be met using multistage counter-current contacters with less than a dozen stages in each process cycle.

Having separated the actinide from the impurities by extraction it is next necessary to back-extract it from the organic to an aqueous phase, allowing the barren solvent to be recycled and once again generating an aqueous actinide solution. This process is often referred to as 'back washing' or 'stripping' but these terms may occasionally be used to describe the scrub section of a process. To avoid confusion, in this work the term 'extraction' will be used to describe the transfer of a solute from the aqueous to the organic phase, the terms 'back wash' or 'back extraction' will refer to the transfer of a solute from the organic to the aqueous phase, and the term 'scrub' will refer to the purification of an organic, or an aqueous, product stream by the back extraction or extraction of contaminants as illustrated for the former case in Figure 31. Since

back washing is the reverse of extraction it involves a change in conditions so as to reduce the actinide distribution coefficient and favour its return to the aqueous phase. Methods of achieving this are illustrated by the solvent extraction purification of uranium from irradiated thermal reactor fuel using TBP. After an extraction cycle, in which oxidation state (III) or (V) actinides, and most of the fission products, have been left in the aqueous raffinate, the organic product solution contains U^{VI} and Pu^{IV}. In order to remove the plutonium the extract is treated with an aqueous reducing agent stream to convert the Pu^{IV} to Pu^{III}, which is then rejected to the aqueous phase. The U^{VI} is not reduced and, provided process conditions are chosen to maintain $D_{U^{VI}}$, remains in the organic phase. Thus the selective oxidation state change allows plutonium to be back-washed independently of the uranium. In order to back-wash the U^{VI} it is necessary to change the process conditions to reduce $D_{U^{VI}}$. The equilibrium constant for UO_2^{2+} extraction by TBP according to equation (110) is given by equation (152). This shows that an increase in the aqueous nitrate

$$K_U = \frac{[UO_2(NO_3)_2(TBP)_2]_{(org)}}{[UO_2^{2+}]_{(aq)}[NO_3^-]^2_{(aq)}[TBP]^2_{(org)}} \tag{152}$$

concentration must be accompanied by an increase in the organic phase uranium concentration if K_U is to be maintained. This is known as the 'salting out' effect and the nitric acid medium in which the actinides are dissolved provides such 'salting' during the initial extraction cycle. Further salting effects can be obtained when necessary by the addition of nitrate salts, particularly $Al(NO_3)_3$, to the aqueous stream. If the organic phase U^{VI} solution is subsequently contacted with an aqueous phase of lower nitrate content, U^{VI} will be transferred back to the aqueous phase because of the loss of the 'salting out' effect. An alternative approach is to contact the actinide containing organic phase with an aqueous phase containing a counter ion which renders the actinide less extractable than with the original counter ion. In the case of the $UO_2^{2+}/NO_3^-/TBP$ system, SO_4^{2-} would provide such an example. An organic scrub section may be incorporated in the back-wash contacter in a similar manner to that used for the extraction. An unloaded solvent feed would enter the scrub section and, on leaving, mix with the loaded organic feed before entering the back-wash section.

The foregoing discussion made the assumption that the value of E_f for a solute remains constant during all stages of the extraction, or the scrub, section of a process. In practice this will not be the case since D_M will vary with the concentration of M in the solution being extracted. A different D_M will thus arise at each stage in the process. Provided sufficient data are available on the distribution behaviour of M, an algebraic description of a multistage extraction process is still possible, although cumbersome. A more convenient means of modelling the process is provided by graphical methods. The distribution behaviour of a single extracting solute may be described by an equilibrium distribution isotherm for the particular conditions used. Such an isotherm is illustrated in Figure 32. This equilibrium curve may be related to the mass balance requirements

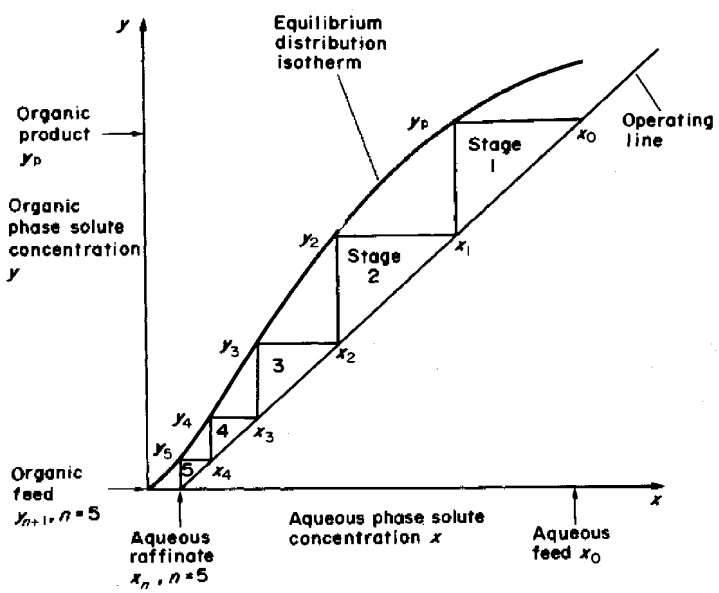


Figure 32 A McCabe–Thiele diagram for a five-stage counter-current solvent extraction process

of a steady state process by means of a McCabe–Thiele construction relating the equilibrium curve to an operating line. Such a construction is also illustrated in Figure 32 for a five-stage counter current process as illustrated in Figure 30c with $n = 5$. The operating line has, as its slope, the ratio of aqueous to organic phase flow rates, V_a/V_o, and is described by equation (153), which

$$y_p - y_{n+1} = \frac{V_a}{V_o}(x_o - x_n) \tag{153}$$

is the overall mass balance requirement of the process. The points (x_i, y_{i+1}) on the operating line refer to the aqueous phase input concentrations to each stage, while the points (x_i, y_i) on the equilibrium curve refer to the organic and aqueous phase output concentrations from each stage after equilibration. The construction relates the phase volume flow ratio, the number of process stages and the organic and aqueous phase feed solute concentrations to the organic product and aqueous raffinate solute concentrations. A typical problem might be to determine the minimum number of stages necessary to achieve a particular organic product composition, y_p, given the aqueous feed solute concentration, x_o, and an acceptable phase volume ratio. A line of slope V_a/V_o passing through (x_o, y_p) would be constructed and the number of stages required to reach or pass the organic phase input concentration, y_{n+1}, determined by stepping off between the operating and equilibrium line. In the case of a solute free organic input, y_{n+1} will be zero.

A similar type of construction may be used to describe the back-washing section of a process except that the operating line will lie above a distribution isotherm plotted with y as ordinate. The slope will be given by V_a/V_o for the back-wash section and will pass through a point defined by the organic phase input concentration and the aqueous phase product concentration, as illustrated in Figure 33a. In the case of a process cycle involving both extract and scrub sections, two operating lines will be necessary. These will have slopes corresponding with the phase volume flow ratios for the extract and scrub sections and will intersect at a point defined by the aqueous feed composition, x_f in Figure 31. Since different conditions will normally prevail in the extract and scrub sections, two different equilibrium distribution isotherms will also be needed to describe the solute behaviour in each section. An example of a construction for such a system is illustrated in Figure 33b. Accounts of the application of McCabe–Thiele constructions in the design of nuclear fuel reprocessing plants are given by Haas[262] and by Wood and Williams.[263]

When more than one solute is involved in the consideration of the process design, the situation becomes much more complex since the extraction behaviours of the different solutes will usually be interdependent. In the case of irradiated thermal reactor fuels the solvent extraction process will be dealing with uranium containing up to *ca.* 4% of fission products and other actinides. These will have only a minor effect on uranium distribution so that a single-solute model may be adequate for process design. However, in some cases nitric acid extraction may compete with UO_2^{2+} extraction and a two-solute model may be needed. In the case of breeder reactor fuels the uranium may contain perhaps 20% of plutonium or thorium. Neptunium or protactinium levels in such fuels may also not be negligible and, under these circumstances, the single-solute

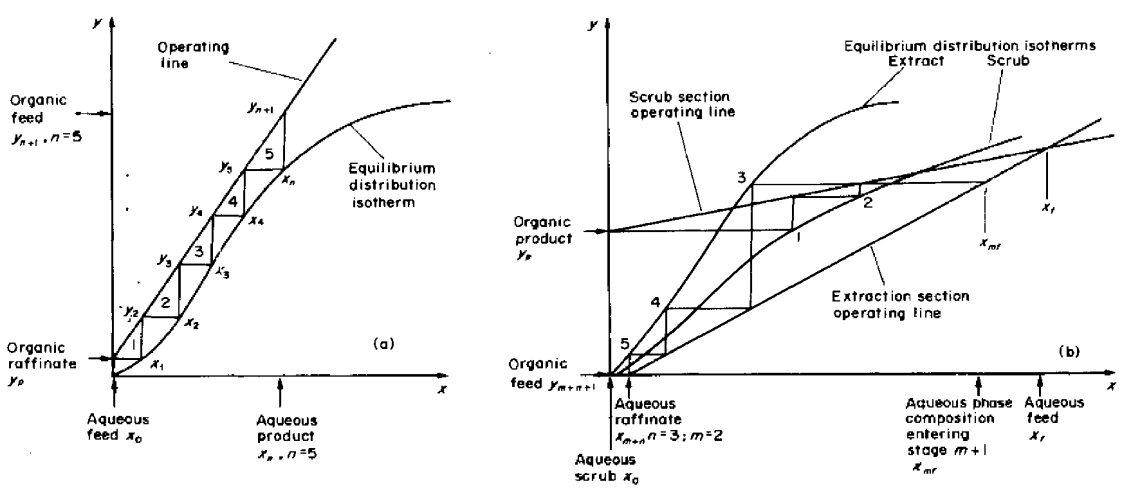


Figure 33 McCabe–Thiele diagrams for (a) a five-stage counter-current back-extraction process and (b) a process involving three stages of extraction and two scrub stages

approximation will not usually be acceptable. Modern computers provide the only realistic means of dealing with design problems of such complexity and programs such as SEPHIS,[264] SOLVEX[265] and QUANTEX[266] have been developed to allow computer modelling of solvent extraction flowsheets. The effective use of such programs requires access to extensive sets of distribution data for the solutes of interest under the conditions prevailing in the process under consideration. The collection of such data, where it does not already exist, may be a formidable task in view of the range of conditions and number of variables involved. The development[267] of the AKUFVE mixer centrifuge system, for the continuous equilibration and separation of liquid phases, has facilitated the collection of distribution data. Coupled with in-line analytical systems this device allows the continuous monitoring of solute concentrations in equilibrated aqueous and organic phases. Stepwise changes in the total solute content of the two phases may be made, allowing the rapid construction of distribution isotherms. Such a device, in conjunction with computer controlled analytical systems, has been adapted[268] for use with plutonium containing solutions. It has been used[269] to obtain data on the $UO_2^{2+}/Pu^{4+}/H^+/NO_3/TBP$ system to support the computer modelling of flowsheets for reprocessing plutonium breeder reactor fuel. Some compilations of distribution data relating to the reprocessing of irradiated reactor fuels have been published[270-273] and empirical equations derived from such data to describe uranium and plutonium distribution behaviour.[274]

The distribution behaviour of the species to be separated is not the only factor affecting the choice of an extractant-diluent combination.[245] The hydrodynamic properties of the solvent phase are important since slow mixing, mass transfer or phase disengagement may be detrimental to process performance. In nuclear fuel reprocessing it is also important for the solvent to have good radiolytic stability and low flammability. Radiolysis products which can complex metal ions and accumulate in the solvent stream can seriously impair plant operation. High-flashpoint low-viscosity hydrocarbon diluents such as odourless kerosene (OK) offer advantages over halocarbon diluents which may give rise to corrosive degradation products. Ketone or ether extractants may also be prone to unwanted side reactions. Methyl isobutyl ketone (MIBK) is prone to peroxidation in air and can be oxidized by nitric acid. Dibutyl carbitol (Butex) will also react with nitric acid under certain conditions.

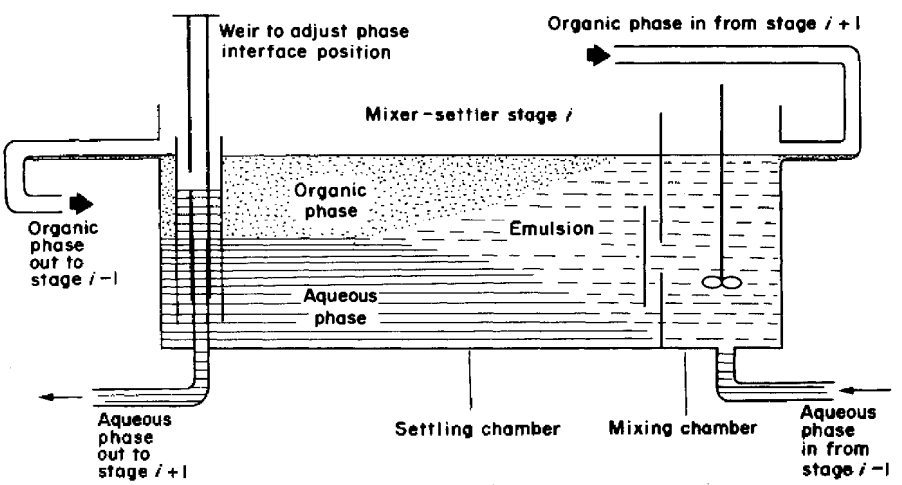


Figure 34 A typical structural arrangement for a mixer-settler contactor stage

The need for simple reliable equipment with a low maintenance requirement and suitability for remote operation places limitations on the type of equipment suitable for equilibrating and separating phases in fuel reprocessing plants. Although mechanically complex devices such as centrifugal contacters have been used, mechanically simple devices such as mixer-settlers or pulsed columns are preferred. A typical mixer-settler arrangement, constituting one stage of a multistage counter current contactor system, is shown in Figure 34. The mixing of the phases may be effected using a mechanical agitator or more simply by pneumatic pulsing of the mixing chamber contents. A typical pulsed column arrangement is shown in Figure 35. In this device the interface between the separated aqueous and organic phases may be set at the top or bottom of the column. In the former case the column is said to be heavy phase continuous and the organic phase is introduced at the bottom of the column through a distributor, which may be vibrated, as a stream of droplets.

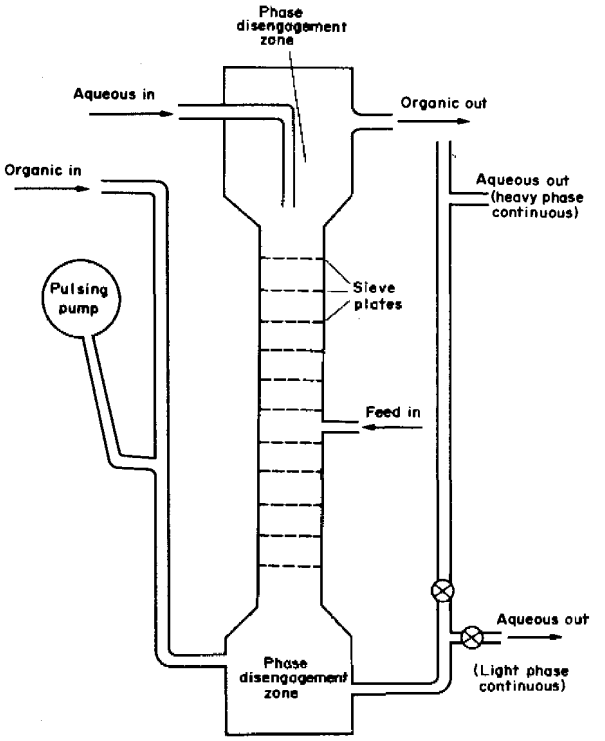


Figure 35 A typical structural arrangement for a pulsed column contacter

These float up, against the bulk aqueous flow down the column, through a series of sieve plates which maintain dispersion and promote good mixing and efficient mass transfer. In the light phase continuous mode the column is filled with the organic solvent through which droplets of aqueous phase fall from a distributor at the top of the column. The column contents are pulsed pneumatically to cause agitation and to prevent the aggregation of droplets of the dispersed phase before they reach the disengagement zone, where the phases separate before passing to the adjacent sections of the process.

Equilibration will not usually be fully established during the passage of two phases through a mixer-settler. An efficiency factor must thus be included in the process design to allow for this. In a simple case where n equilibrium extraction stages are required, an efficiency of 67% for the mixer-settler/mixed phase combination involved would imply the need for $n/0.67 = 1.5n$ stages in the plant. In the case of the pulsed column, calculations must be carried out to define the height of a transfer unit, that is the column height required for the two phases to reach equilibrium in a hypothetical one-stage contact. Once this value is known it may be multiplied by the number of equilibrium stages required by the process, thus defining the minimum column height necessary. Mixer-settlers and pulsed columns are well suited for use in fuel reprocessing plants since neither need contain any moving parts. The construction of these devices allows pneumatic pulsing and hydrodynamics to effect the necessary mixing and phase separation is effected by gravity alone.

65.2.4.3 Solvent extraction processes

(i) Thermal reactor fuels

Although TBP is the extractant now used in all plants reprocessing power reactor fuel, in the past other extractants have also been successfully used. In particular, MIBK, also known as 'Hexone', was used in the Redox process for separating uranium and plutonium at Hanford, USA, during the period 1951–66. During the same period, dibutyl carbinol, known as 'Butex' ($C_4H_9OCH_2CH_2OCH_2CH_2OC_4H_9$) was used for this purpose at the Windscale plant in the UK. Amine extractants have also been used in actinide separations but are better suited for oxidation state (IV) actinide nitrate extraction than for $UO_2(NO_3)_2$. Consequently they have not found prominence in fuel reprocessing where uranium is the major component. Their main application comes in separating higher actinides after they have been removed from the uranium.

MIBK is a poorer extractant of oxidation state (VI) actinide nitrates than Butex or TBP,[275] and is not an effective extractant for oxidation state (IV) actinides at acidities below *ca.* 1 M HNO_3. However, MIBK will extract $UO_2(NO_3)_2$ and $PuO_2(NO_3)_2$ from aqueous streams salted with nitrate and this provided the basis of the Redox process shown in outline in Figure 36. The salting agent used was $Al(NO_3)_3$ while $K_2Cr_2O_7$ was present in the feed stream to convert Pu^{4+} to PuO_2^{2+} according to equation (154). The formal potential for the oxidation of Pu^{4+} to PuO_2^{2+} in 1 M HNO_3 is quoted[277] as 1.1 V and is more cathodic than the potential for oxidizing Pu^{4+} to PuO_2^{+}.

$$3Pu^{4+} + Cr_2O_7^{2-} + 2H^+ \rightarrow 3PuO_2^{2+} + 2Cr^{3+} + H_2O \quad (154)$$

$$2PuO_2^{+} + 4H^+ \rightleftharpoons Pu^{4+} + PuO_2^{2+} + 2H_2O \quad (155)$$

Furthermore, PuO_2^{+} disproportionates rapidly below pH 2 according to equation (155),[278,279] so that PuO_2^{+} was not a significant component of the feed stream. Two different flowsheets were developed for the Redox process.[280,281] The acid flowsheet utilized an aqueous feed containing 2 M $UO_2(NO_3)_2$, 0.3 M HNO_3 and 0.1 M $Na_2Cr_2O_7$ in conjunction with an aqueous scrub containing 1.3 M $Al(NO_3)_3$. This gave an organic product containing 0.5 M $UO_2(NO_3)_2$ and 0.2 M HNO_3.

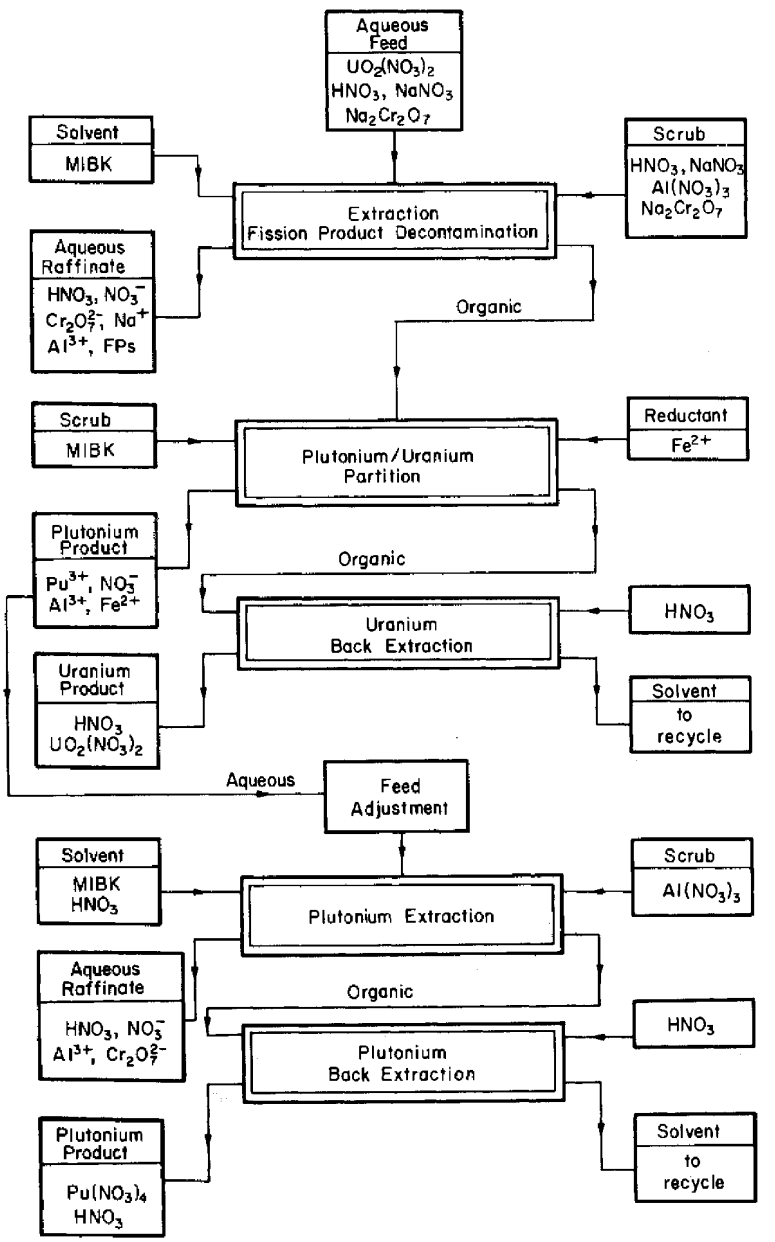


Figure 36 An outline flowsheet for the Redox process

In the acid deficient flowsheet the acid released from $Al(NO_3)_3$ hydrolysis was neutralized to give an organic product containing 0.5 M $UO_2(NO_3)_2$ but only 0.05 M HNO_3. The $Al(NO_3)_3$, $Na_2Cr_2O_7$ and FPs were retained in the aqueous raffinate from the extraction section, while the organic product was passed to the U/Pu partition contacter.

In order to separate the uranium and plutonium the PuO_2^{2+} was reduced to Pu^{3+}, which was not extracted by MIBK and was thus held in the aqueous phase. The choice of a reducing agent for plutonium is rather important, and is discussed in more detail below in relation to the Purex process. In the Redox process, 0.05 M aqueous iron(II) sulfamate salted with 1.3 M $Al(NO_3)_3$ was used, the reduction of PuO_2^{2+} by Fe^{2+} proceeding according to equation (156). The products

$$PuO_2^{2+} + 3Fe^{2+} + 4H^+ \rightarrow Pu^{3+} + 3Fe^{3+} + 2H_2O \quad (156)$$

from the partition contacter were thus an organic $UO_2(NO_3)_2$ stream and an aqueous $Pu(NO_3)_3$ stream. The uranium was back washed from the organic stream by 0.1 M HNO_3, with no added salting agents, to give an aqueous product containing *ca.* 0.85 M $UO_2(NO_3)_2$. To achieve the required decontamination factor this was passed to a second, and where necessary a third, cycle of extract and back wash. The $Pu(NO_3)_3$ stream was also passed to a second cycle of extract and back wash to remove the aluminium, sulfate and chromium present in the first cycle aqueous plutonium product. Again dichromate oxidation and $Al(NO_3)_3$ salting were necessary to give an organic $PuO_2(NO_3)_2$ extract. The plutonium was then back washed from this using 0.1 M HNO_3 to give a purified plutonium nitrate product.

The acid flowsheet was found to give a better plutonium recovery than the acid deficient process. However, the latter gave better decontamination from gross β activity, especially for uranium, with $DF_{\beta\gamma}$ figures of 3.1×10^5 for uranium and 2×10^6 for plutonium being attained after two cycles. Comparable values for the acid flowsheet were respectively 1.6×10^4 and 6.3×10^5. Although the Redox process was used successfully for a number of years,[280] it had major disadvantages. MIBK is toxic and of low flash point; it is also unstable towards high HNO_3 concentrations so that added $Al(NO_3)_3$ was necessary to provide a salting effect. Coupled with the use of $Na_2Cr_2O_7$ as oxidant, this added substantial amounts of aluminum and chromium to the high level waste output from the plant, thus increasing waste management costs. The Butex process[282] avoided the need for salting with $Al(NO_3)_3$ by using higher nitric acid concentrations to provide a salting effect. This was possible because Butex is less reactive towards HNO_3 than is MIBK. The need to oxidize the plutonium to PuO_2^{2+} was also eliminated since Butex will extract Pu^{4+} well from aqueous nitrate media. The distribution coefficients[283] for uranium and plutonium between Butex and 3 M HNO_3 are $D_{U^{VI}} = 1.5$, $D_{Pu^{VI}} = 1.8$ and $D_{Pu^{IV}} = 7$. The process flowsheet is shown in outline in Figure 37. The acidity of the solution from the fuel dissolution step was adjusted to 3 M HNO_3 prior to extraction with Butex to give an organic phase containing UO_2^{2+} and Pu^{4+}. Neutralization with ammonia followed by reduction with $Fe(SO_3NH_2)_2$ gave a mixed phase system containing UO_2^{2+} and Pu^{3+} in 0.5 M HNO_3, from which the Pu^{3+} was back extracted with 8 M NH_4NO_3 solution. $D_{Pu^{III}}$ between Butex and 8 M NH_4NO_3 containing 0.2 M HNO_3 is less than 2×10^{-3} so that only 0.02% of the plutonium present remained with the uranium in the organic phase. The aqueous plutonium stream was then passed to a plutonium purification cycle. This involved the oxidation of Pu^{3+} to Pu^{4+} using $Na_2Cr_2O_7$ followed by a cycle of extraction with Butex and back washing with 0.05 M HNO_3. A second cycle of plutonium purification was effected using extraction with 20% TBP in OK and an aqueous 0.25 M HNO_3 back wash. The organic phase uranium stream from the first cycle partition section was back washed with 0.05 M HNO_3 to give an aqueous uranyl product stream, which also contained NH_4NO_3. This was concentrated to 300 g dm^{-3} uranium and stored for 6 months to allow some decay of the ^{106}Ru and ^{103}Ru present. The solution was then partly neutralized and treated with aqueous $Fe(SO_3NH_2)_2$ prior to extraction with Butex to give an organic phase containing uranium further decontaminated from FPs and plutonium. An aqueous back wash with 0.1 M HNO_3 then afforded the aqueous uranyl nitrate product.[282]

The major disadvantage of the Butex process was the poor fission product decontamination achieved in the first cycle. This arose primarily from the extraction of $Ru(NO)(NO_3)_3$ by Butex under the conditions used. Some decontamination factors for specific FPs are given in Table 11. These show the marked improvement in DF_{Ru} obtained by using 20% TBP in OK for the second plutonium purification cycle. The maximum uranium concentration acceptable in the Butex process was limited to 150 g dm^{-3} because of the risk that $UO_2(NO_3)_2 \cdot C_{12}H_{26}O_3$ might precipitate at higher concentrations. Although Butex did not normally react with nitric acid under process conditions, vigorous reactions have been known to occur. They apparently involved butanol formed by the

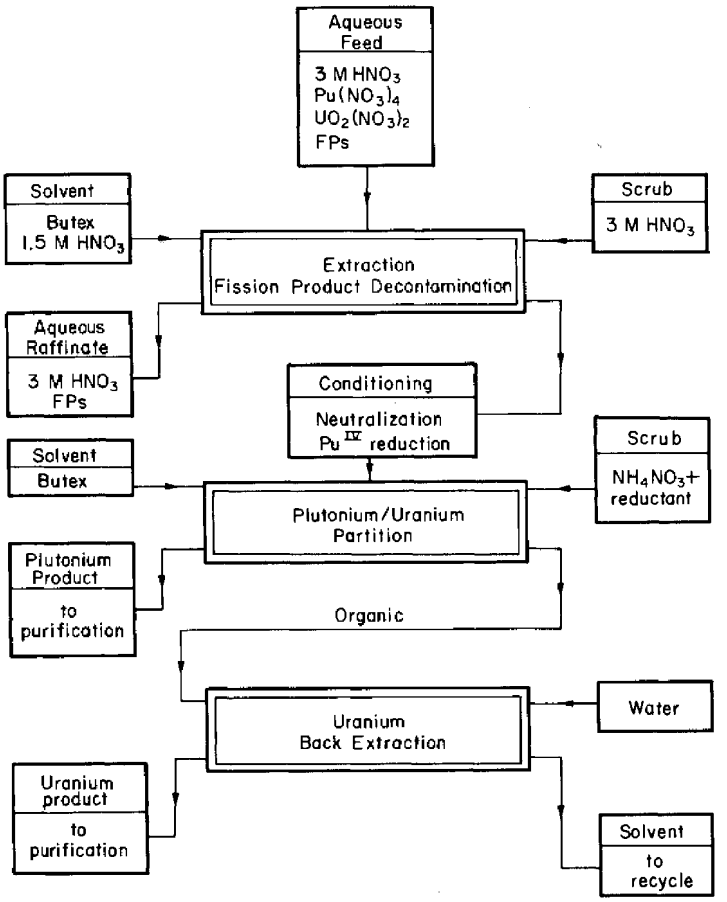


Figure 37 An outline flowsheet for the Butex process

Table 11 Some Decontamination Factors in the Butex Process

	Decontamination factors by element				
	Ru	*Zr*	*Nb*	*Ce*	*Pu*
First process cycle extract	10	4000	400	10^5	—
First U purification cycle	200	200		—	40
First Pu purification cycle (Butex)	15	30	130	10	—
Second Pu purification cycle (20% TBP/OK)	2000	10	—	—	—

degradation of Butex and were catalyzed by nitrous acid.[284] The possibility of such reactions represents another disadvantage in the use of Butex. Although the combined use of Butex and TBP in plutonium production was successful, it is advantageous to use a single solvent throughout a process. This eliminates any problem which might arise from cross contamination of one extractant with another. Such considerations, combined with its effectiveness in actinide separation and decontamination processes, have led to the emergence of TBP as the dominant extractant in modern power reactor fuel reprocessing.

Many variants of the Purex (Plutonium Uranium Reduction Extraction) process[285] based on TBP extraction have been developed but a basic outline flowsheet is illustrated in Figure 38. This shows the so-called 'early split' flowsheet most commonly used in existing plants. It involves the separation of the uranium and plutonium using two different back-extractant streams during the first solvent extraction cycle. Additional solvent extraction cycles are then carried out independently on the uranium and plutonium streams to effect further purification. An alternative arrangement is the 'late split' flowsheet used at the Cap La Hague plant in France, and the

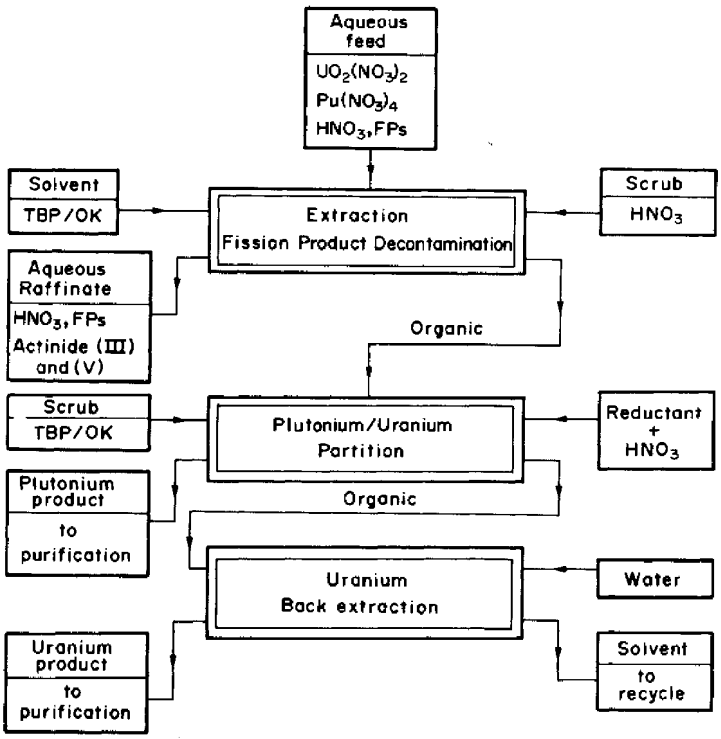


Figure 38 An outline flowsheet for the Purex process

Windscale II plant in the UK. In this the uranium and plutonium are back-extracted together in a first cycle of decontamination. They are then separated in a second cycle of solvent extraction and independent back-extraction. The factors affecting the choice of flowsheet type have been reviewed and criticality control is an important consideration in the process design.[286]

A second important variant in the Purex process is the choice of a reducing agent to convert Pu^{IV} to Pu^{III} in the U/Pu separation cycle. In the older plants, iron(II) sulfamate was commonly used. However, this reagent adds iron and sulfate to process waste streams and more recent plant designs have selected reductants which do not add extraneous materials to radioactive wastes. The Marcoule and Cap la Hague plants in France utilize U^{IV} for this purpose. The disadvantage of this reagent is that it increases the uranium inventory in the plant and requires a greater plant capacity. Electrolytic reduction does not have this disadvantage and is incorporated in the design of the Barnwell plant in the USA. Hydroxylamine has also been considered since it is readily destroyed in nitric acid media, giving N_2O.[287,288] However, the kinetics of Pu^{IV} reduction by NH_2OH are unsuitable for process streams of high acidity, as may be encountered in the first extraction cycle.

TBP is a sufficiently powerful extractant for actinides that it may be used in diluted form. Dilution improves the hydrodynamic properties of the solvent, allowing more complete and rapid phase disengagement. Typically concentrations of 20–30 v/o TBP in OK are used in process flowsheets. Although TBP is relatively stable as an extractant, radiolysis does lead to the formation of some acidic phosphate esters, HDBP and H_2MBP, which can impair process performance.[289] An aqueous alkali wash of the recycled solvent is usually carried out to remove those by products. Radiolytic degradation of the diluent in the presence of nitric acid can result in the formation of hydroxamic acids,[290] which can lead to fission product retention by the organic phase. Again the solvent wash is used to prevent the accumulation of such species. A comprehensive account of the industrial utilization of TBP has recently been published.[291]

(ii) Chemistry of the fission products in the Purex process

During the dissolution of the irradiated fuel in nitric acid the acidity of the solution will fall from 7–8 M HNO_3 to 3–5 M HNO_3. The metals present will be dissolved as their nitrate salts and under these conditions the Group I and II metals, principally cesium, strontium and barium, will then be present as solvated mono- or di-cations respectively. These do not form extractable

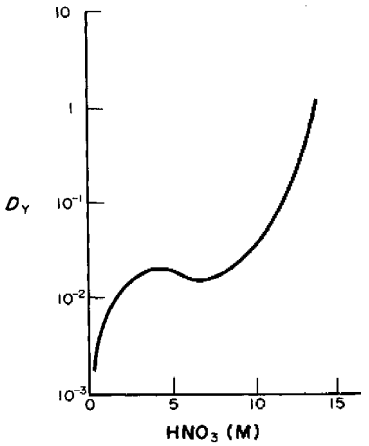


Figure 39 The extraction of yttrium from HNO_3 by 19% TBP/OK[417]

adducts with TBP and their distribution coefficients[292] between 30% TBP/OK and 1 M HNO_3 are less than 10^{-3} with $D_{Cs} < 10^{-4}$.

Yttrium and the lanthanide FPs, mainly cerium, praseodymium and promethium, will be present in the dissolver solution as trications, which are poorly extracted by TBP/OK. Distribution coefficient measurements show[293] that the trisolvates are extracted according to equation (157).

$$Ln^{3+}_{(aq)} + 3NO_3^-{}_{(aq)} + 3TBP_{(org)} \rightleftharpoons Ln(NO_3)_3 \cdot 3TBP_{(org)} \quad (157)$$

The variation in D_{Ln} with nitric acid concentration is illustrated in Figure 39 for yttrium. The lanthanides all exhibit broadly similar behaviour but have distribution coefficients which are lower than D_Y at high acidities but become greater than D_Y at low acidity. The values of D_{Ln} for the TBP/OK/HNO_3 system increase with increasing atomic number for Ln. A typical value for D_{Ln} under process conditions might be *ca.* 10^{-2}. The decrease in D_Y at intermediate acidities has been attributed to competition for TBP by HNO_3, while the steep increase with increasing acidity at low HNO_3 concentrations reflects the salting effect of the nitrate ion. IR studies[294] indicate that the complexes $[Ln(NO_3)_3(TBP)_3]$ contain nine-coordinate metal ions bound to three TBP phosphoryl oxygens and six oxygens from three bidentate nitrate ligands.

The behaviour of ruthenium presents a far more complicated problem because of the variety of ruthenium species which may be present in the solution, and the relatively slow kinetics of their interconversion. The ruthenium is present in dissolver solutions as complexes of the very stable $\{Ru(NO)\}^{3+}$ ion. The coordination chemistry of ruthenium nitrosyls has been reviewed in general[295] and also in particular relation to fuel reprocessing.[10,296,297] The species present in the solution may be represented by the general formula $[Ru(NO)(NO_3)_x(NO_2)_y(OH)_2(H_2O)_{5-(x+y+z)}]^{3-(x+y+z)}$. In solutions of high nitrate and low nitrite concentration, species having $y = z = 0$ and $x \leq 4$ predominate. At low nitrate concentrations hydroxy species with $x = y = 0$ and $z \leq 2$ or $x = z = 1$ and $y = 0$ may also be found.[298,299] The relative proportions of the different nitrate complexes vary with acidity as shown[300] in Figure 40. When appreciable concentrations of nitrite are present, nitrito complexes may form and species having $x = 0$, $y = 4$, $z = 1$; $x = 0$, $y = 2$, $z = 1$; $x = 0$, $y = 3$, $z = 0$; and $x = 2$, $y = 1$, $z = 0$ have been identified.[301] The structure of $Na_2[Ru(NO)(NO_2)_4(OH)] \cdot 2H_2O$ has been determined[302] by neutron diffraction techniques and it adopts the octahedral geometry proposed for all the $\{Ru(NO)\}^{3+}$ complexes discussed above. The complex contains a linear nitrosyl group *trans* to the hydroxide ligand as shown in Figure 41. Counter pressure column electrophoresis measurements[298] have shown that the nitric acid solutions used in laboratory investigations contain $\{Ru(NO)\}^{3+}$ complexes representative of those found in medium and high activity aqueous raffinates from the Purex process. The kinetics of interconversion of the various nitrato species present in nitric acid have been investigated[300,303,304] and the half times[304] for the nitration in 10 M HNO_3, or aquation in 0.45 M HNO_3, of the species present in aqueous media at 0 °C are summarized in Figure 42. These equilibria partially account for the complicated time dependent extraction behaviour of ruthenium since the different species have differing distribution coefficients.

In plant solutions, up to 70% of the $\{Ru(NO)\}^{3+}$ may be in the form of inextractable nitrito complexes.[305] However, as the nitrato species extract the mass action affect of the nitrate present may lead to the substitution of nitrite with nitrate, even though the former gives the more

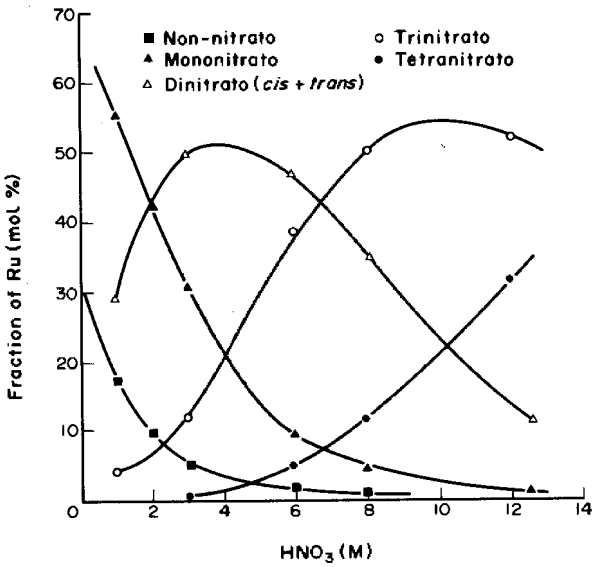


Figure 40 Variations in the relative quantities of different ruthenium nitrosyl complexes in nitric acid at 20 °C for 10^{-3} M total ruthenium[10,300]

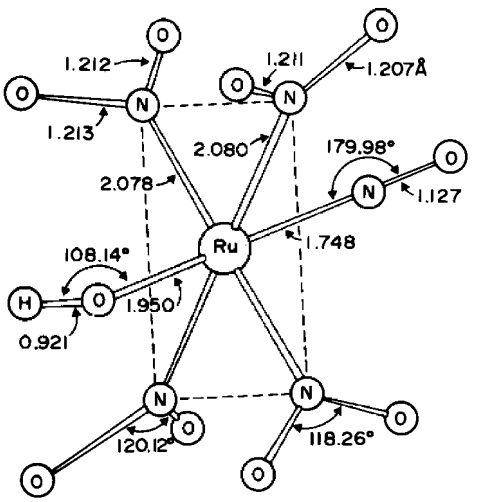


Figure 41 The structure of $Na_2[Ru(NO)(NO_2)_4(OH)]$[302]

stable $\{Ru(NO)\}^{3+}$ complex. This would give rise to the observed[306] increase in D_{Ru} with time. Distribution measurements on the nitrato complexes have shown[307] that cationic complexes are not extracted to any extent but that with 30% TBP/OK both $[Ru(NO)(NO_3)_3(H_2O)_2]$ and $[Ru(NO)(NO_3)_4(H_2O)]^-$ can give D_{Ru} values in the range 1–10 for aqueous phase nitric acid concentrations of 3–5 M. The mechanism of extraction appears[296,307–309] to involve the formation of labile TBP adducts such as $[Ru(NO)(NO_3)_3(H_2O)_2]\cdot 4TBP$ and $[H_3O\cdot 3TBP]^+[Ru(NO)(NO_3)_4(H_2O)]^-\cdot 2TBP$ in which the phosphoryl oxygens solvate the protons of the water ligands. These are then transferred to the organic phase, where the TBP slowly replaces inner sphere nitrato or aquo ligands to give $[Ru(NO)(NO_3)_3(TBP)_2]$ as the neutral extracted species. Thus although the tetranitrato complex is extractable, it is in fact the trinitrato complex which is the ultimate organic phase complex and gives rise to a higher D_{Ru} than for the initially extracted species. It is likely that, in the organic phase, TBP may first replace the water in the labile coordination site *trans* to the NO ligand. Subsequent slow rearrangement to a nonlabile position *cis* to the NO ligand would then lead to the formation of a complex which was difficult to back extract from the solvent. A kinetically slow rearrangement of this type would thus account for the difficulties encountered in back-extracting ruthenium. The extraction of $\{Ru(NO)\}^{3+}$ into TBP/OK was found[310] to reach a maximum at 1 M HNO_3 in the aqueous phase. The addition of

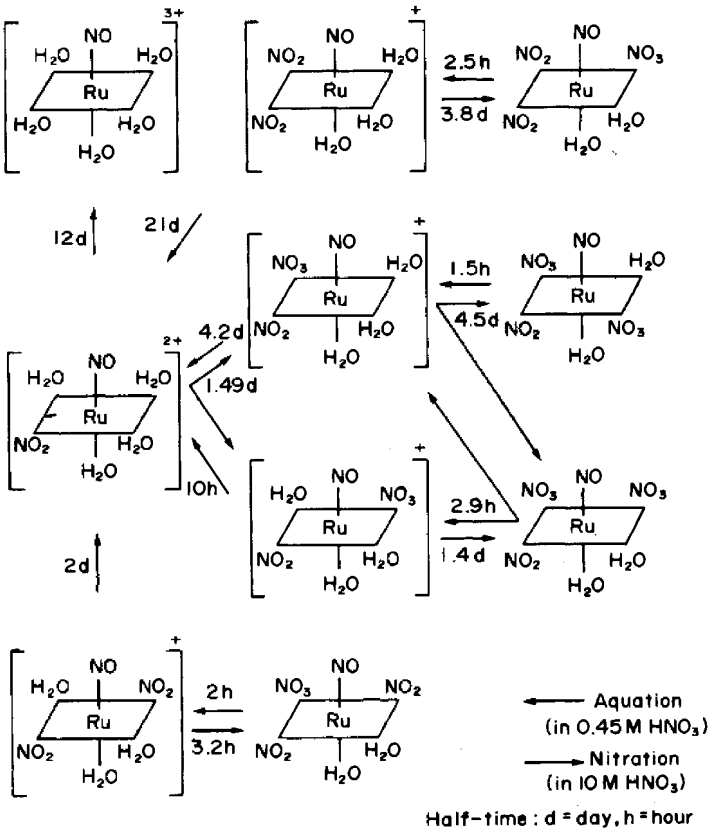


Figure 42 The interconversion of ruthenium nitrosyl complexes in nitric acid at 0 °C[304]

$NaNO_3$ increased D_{Ru} further while HDBP had a synergic effect on $\{Ru(NO)\}^{3+}$ extraction by TBP. This latter observation indicates another mechanism by which ruthenium may be extracted into and retained by the organic phase.

Despite the considerable body of knowledge now available on the extraction chemistry of ruthenium, it remains a problematic element for fuel reprocessors. A variety of means[10] may be used to render the ruthenium less extractable. These include the addition of reagents such as oxalate or thiourea, the oxidation of Ru^{III} to inextractable Ru^{IV} or the addition of nitrogen dioxide to retain more $\{Ru(NO)\}^{3+}$ in the form of nitrito complexes of low D_{Ru}. However, such treatments may have undesirable effects on plant operation. It is possible to attain high decontamination factors for ruthenium over several process cycles, the penalty being that the ruthenium will appear in several waste streams, not just the HAW from the first decontamination cycle.

Zirconium is the principal FP to arise in oxidation state (IV). Where Zircaloy clad fuel is involved, nonradioactive zirconium isotopes may also be present from fuel can residues. As with ruthenium, there may be a variety of nitrato complexes present in the solution including the aquated complexes $Zr(NO_3)_x^{4-x}$, where $x = 1$-6, and hydroxy nitrato complexes. However, species containing ZrO^{2+} are not expected to be present since this ion is unstable in aqueous media and is rapidly hydrated[311] to $Zr(OH)_2^{2+}$. The extraction chemistry is further complicated[312] by the formation of inextractable polymeric species when the Zr^{IV} concentration exceeds *ca.* 10^{-2} M. An example of such oligomerization is afforded by the $[Zr(OH)_2(H_2O)_4]_4^{8+}$ ion which contains four Zr^{4+} ions in a square arrangement linked by two μ-OH ligands on each square edge.[313] Four water molecules complete the Zr^{4+} coordination sphere in an approximately D_{2d} dodecahedral geometry.

The extraction of Zr^{IV} by pure TBP/OK phases increases rapidly with aqueous phase acidity so that D_{Zr} for 19% TBP/OK increases from *ca.* 10^{-2} at 0.5 M HNO_3 to *ca.* 10^2 at 13 M HNO_3.[314] Satisfactory decontamination from zirconium can thus be achieved using aqueous phase acidities in the range 2–3 M where D_{Zr} will be *ca.* 0.1. The extraction reaction was described[315] by equation (158) but more recent work[316] also indicates the presence of $Zr(OH)_2(NO_3)_2 \cdot 2TBP$ and $Zr(OH)$-

$$Zr(OH)_2^{2+}{}_{(aq)} + 2H^+{}_{(aq)} + 4NO_3^-{}_{(aq)} + 2TBP_{(org)} \rightleftharpoons Zr(NO_3)_4 \cdot 2TBP_{(org)} + 2H_2O_{(aq)} \quad (158)$$

$(NO_3)_3 \cdot 2TBP$ when TBP concentrations below 0.3 M are in contact with nitrate concentrations below 0.6 M. There is also evidence for a monosolvate species.[317,318]

Zirconium can give rise to separation problems if the TBP radiolysis products HDBP and H_2MBP are allowed to accumulate. At low Zr^{4+} concentrations, $Zr(NO_3)_2(DBP_2H)_2$ is extracted from nitric acid by HDBP.[319] At higher concentrations, $Zr(NO_3)_2(DBP)_2$ may form and precipitate as a polymeric solid. Such precipitates may act as emulsion stabilizers, preventing phase disengagement and impairing process performance. The addition of H_2MBP to extracts of Zr^{4+} into TBP containing HDBP led to the formation[320] of a solid of composition $Zr(OH)_x(NO_3)_y \cdot DBP \cdot MBP$, where $x+y=1$. The extraction behaviour of Zr^{4+} appeared to be determined by the HDBP present but its retention and precipitation were determined by H_2MBP even where an excess of HDBP over H_2MBP was present. H_2MBP alone gave rise to gelatinous solids containing hydrated $Zr(MBP)_2$. IR studies[321] have also confirmed the presence of MBP and DBP in solids precipitated by aged organic phase Zr^{4+} extracts.

Other solvent degradation products derived from the diluent as well as from TBP may arise. Butyl lauryl phosphoric acid (HBLP) has been used[322] as a model for diluent derived diesters of phosphoric acid[322] and at concentrations above 2×10^{-4} M enhances Zr^{4+} extraction by TBP. HBLP is not removed by alkali washing of the solvent but BLP^- is transferred into water at low ionic strength. Dialkylphosphorane complexes of Zr^{4+} may also arise from irradiation and can stabilize emulsions.[323] Diluent derived hydroxamic acids are present at too low a concentration (10^{-8}–10^{-9} M) to completely account for the extent of zirconium retention which occurs in irradiated TBP/OK extractions,[324] although Zr^{4+} does form hydroxamate complexes.[325] The relative order of extractability of metal cations by dialkyl phosphoric acids was found[305] to be $Zr^{4+} > Pu^{4+} > UO_2^{2+} > \{Ru(NO)\}^{3+} > Nb^V$. However, the mass action effect of the UO_2^{2+} present is to complex virtually all the HDBP and some of the H_2MBP present. The residue will then largely be complexed by Zr^{4+} and Pu^{4+}. A single pass of solvent through a pulsed column contactor in the first decontamination cycle might give rise to *ca.* 10^{-5} total alkyl phosphoric acids.[306] Under such conditions, FP decontamination is not significantly affected.

Niobium occurs in oxidation state (V) in the dissolver solution and does not extract into pure TBP/OK phases to a significant extent. Values of *ca.* 5×10^{-4} have been quoted[327,328] for D_{Nb} between 20% TBP/OK and 2 M HNO_3. Inextractable polymeric hydroxy complexes of Nb^V are formed but the presence of silicates[329] or HDBP[330] can lead to some extraction of niobium species. A model for the extraction by HDBP is provided by HBLP, which was thought to extract Nb^V according to equation (159) on the basis of IR studies.[331] HDBP might similarly lead to some synergic extraction of Nb^V in TBP/OK but, as mentioned above, free HDBP will not be available in the first process cycle,[326] and in practice problems do not usually arise with niobium.

$$Nb(OH)_{5(aq)} + HBLP_{2(org)} \rightleftharpoons Nb(OH)_4BLP \cdot HBLP_{(org)} + H_2O_{(aq)} \quad (159)$$

Molybdenum provides an example of a fission product which would appear in the dissolver solution in oxidation state (VI). However, the half lives of the molybdenum isotopes produced are sufficiently short for decay processes largely to eliminate this element before fuel reprocessing is undertaken. The extraction of Mo^{VI} by TBP from aqueous nitrate solutions of pH 0.5–3.0 has been investigated.[332] It was found that at Mo^{VI} concentrations above 10^{-4} M, slow aqueous phase polymerization reactions gave rise to time dependent extraction behaviour. Thus $D_{Mo^{VI}}$ between TBP and a solution containing 1.0 M KNO_3 and 1.5×10^{-4} M Mo^{VI} at pH 3 rose to 0.1 over a period of 12 hours. At Mo^{VI} concentrations below 10^{-4} M, equilibrium was rapidly attained and in this case $D_{Mo^{VI}}$ was at a maximum of 0.08 between pH 0.5 and pH 1.0, falling off steeply at higher pH values. The extracted species was found to be $Mo(OH)_6 \cdot HNO_3$.

A far more important fission product is ^{99}Tc, which appears in oxidation state (VII) as TcO_4^- in the dissolver solution. In the past, ^{99}Tc was not a major concern because of its low specific activity and the low energy of its β-emission. However, much larger quantities of this isotope are now arising from high burn-up power reactor fuel. Furthermore it has a long half-life (2.1×10^5 y) and the dissolved TcO_4^- ion is highly mobile in the environment. These factors combine to make ^{99}Tc extremely important as a component of HAW in long-term storage because of its potential environmental effects.[333] Reactions of TcO_4^- with reductants used for plutonium valence control may also have implications in process design.[11]

The extraction of TcO_4^- from nitric acid media by TBP/OK has been reported to follow equation (160) in the absence[334] of UO_2^{2+} and equation (161) in the presence[334,335] of UO_2^{2+}. The values of $D_{Tc^{VII}}$ between nitric acid and TBP/OK were found[336,337] to increase with HNO_3 concentration to a maximum value between 0.6 and 1.0 M HNO_3 before falling off because of competition

between HNO_3 and $HTcO_4$ for the available TBP. At 25 °C the maximum $D_{Tc^{VIII}}$ value with 30% TBP/*n*-dodecane was 0.9, falling to 0.18 at 60 °C. The corresponding values for 20% TBP/*n*-dodecane were some four times smaller. Values of 75 J mol^{-1} for ΔG and -197 J mol^{-1} K^{-1} for ΔS were obtained for the extraction reaction.[336] In the absence of nitric acid the extracted species was found to be $HTcO_4 \cdot TBP \cdot (TBP \cdot H_2O)_3$, a similar species having been proposed to account for the extraction of $HReO_4$ by TBP.[338-340]

$$H^+_{(aq)} + TcO_4^-_{(aq)} + 3TBP_{(org)} \rightleftharpoons HTcO_4 \cdot 3TBP_{(org)} \quad (160)$$

$$UO_2^{2+} + NO_3^-_{(aq)} + TcO_4^-_{(aq)} + 2TBP_{(org)} \rightleftharpoons UO_2(NO_3)(TcO_4) \cdot 2TBP_{(org)} \quad (161)$$

The effect of added nitrite, nitrate and uranyl ions on TcO_4^- extraction has been studied.[338] Aqueous $NaNO_2$ concentrations between 10^{-3} and 10^{-2} M had little effect on $D_{Tc^{VII}}$ but the presence of NH_4NO_3 concentrations from 1 to 4 M was found to depress $D_{Tc^{VII}}$ because of the salting-out effect on aqueous phase TBP. Added UO_2^{2+} ions gave rise to $D_{Tc^{VII}}$ values which decreased with increasing HNO_3 concentration and did not show the maximum at 0.6 M HNO_3 observed in the absence of UO_2^{2+}. Studies of the extraction of $UO_2(TcO_4)_2$ itself have shown[337] that Tc^{VII} extraction according to equation (162) could occur. Thus in the $UO_2^{2+}/TcO_4^-/NO_3^-/H_2O$-TBP/OK system, different species were present in the organic phase depending upon the relative concentrations of the aqueous phase components. At aqueous UO_2^{2+} concentrations above 10^{-2} M, $UO_2(TcO_4)_2 \cdot 2TBP$ was extracted, while at concentrations below 3×10^{-3} M, $UO_2(NO_3)_2 \cdot 2TBP$ was extracted along with $HTcO_4 \cdot 3TBP$. The mixed anion complex $UO_2(NO_3)(TcO_4) \cdot 2TBP$ was only observed in the organic phase under a limited range of conditions, *viz.* for UO_2^{2+} concentrations between 3×10^{-4} and 3×10^{-3} M at acidities between 0 and 0.1 M or UO_2^{2+} concentrations between 10^{-3} and 10^2 M at acidities between 0.1 and 1.0 M. This species was not found at acidities in excess of 1 M. However, studies using 6 M HNO_3 gave results which were consistent with $UO_2(NO_3)(TcO_4)_2 \cdot 3TBP$ as the stoichiometry of the extracted species. The presence of hydrazine nitrate or iron(II) sulfamate at concentrations between 10^{-3} and 10^{-2} M was not found[341] to affect $D_{Tc^{VII}}$ significantly while DBP had only a small effect. Empirical numerical equations have been developed[341,342] to describe the extraction behaviour of TcO_4^- and UO_2^{2+} present together under conditions appropriate to the Purex process.

$$UO_2^{2+}_{(aq)} + 2TcO_4^-_{(aq)} + 2TBP_{(org)} \rightleftharpoons UO_2(TcO_4)_2 \cdot 2TBP_{(org)} \quad (162)$$

The extractability of TcO_4^- in the presence of UO_2^{2+} may result in a few percent of the ^{99}Tc present following the uranium stream.[10,11] Furthermore, the conditions which favour the separation of Np^V from U^{VI} may promote Tc^{VII} extraction to give low DF_{Tc} values. An additional complication arises from the reactions of TcO_4^- with reductants and stabilizers used to produce Pu^{III} in the U/Pu separation section of the process.[343] These reactions may have a detrimental effect on U/Pu separation. They also give rise to lower oxidation state technetium species which are poorly extracted and may compromise the purity of the plutonium product stream.[11] Recent studies have also shown[343] that zirconium and technetium may coextract in the first Purex cycle, leading to lower DF_{Tc} values than previously expected. The extracted species is a 1:1 TBP solvate possibly of formula $Zr(NO_3)_3(TcO_4) \cdot TBP$. Careful process design and control are thus necessary to achieve acceptable DF_{Tc} values for high burn-up fuels and the control of technetium behaviour in the Purex process still presents a major challenge to fuel reprocessors.

Ruthenium provides the only example of a fission product which might arise in oxidation state (VIII) as RuO_4. The formation of this compound presents special problems because of its organic phase solubility, volatility and reactivity. Fortunately, conditions in Purex process streams do not normally give rise to RuO_4 since temperatures above 70 °C are necessary for RuO_4 formation at nitric acid concentrations below 8 M. Furthermore, the presence of nitrous acid or nitrogen oxides would lead to the rapid reduction of Ru^{VIII}. However, RuO_4 may arise when nitric acid solutions are evaporated or thermally denitrated, for example when HAW is vitrefied to produce solid waste.[11] Where the formation of RuO_4 is possible it will be necessary to design process off-gas facilities which will absorb it. In fact the thermal oxidation of irradiated oxide fuel in the 'Voloxidation' process[344] may be used as a means of removing volatile fission products, including ruthenium, from spent fuel.

(iii) Chemistry of the actinides in the Purex process

Several general accounts of actinide chemistry are available,[207,242,345,346] including those in specific volumes of the Gmelin Handbook on chemistry in solution,[347,348] the solvent extraction

of uranium[272] and irradiated fuel reprocessing.[349] The solution chemistry of the actinides has also been reviewed by Ahrland *et al.*[90] and, more recently, with the emphasis on thermodynamic considerations, by Choppin.[350] In addition to uranium and plutonium, spent thermal reactor fuel will also contain significant amounts of neptunium along with some americium and curium.[13] These will be present in the dissolver solution in oxidation states which depend upon the element and whether there has been any chemical conditioning of the nitric acid solution, for example with nitrogen oxides or fluoride. After dissolution the solution will contain little nitrous acid.[11] However, conditioning with nitrogen oxides is often carried out to convert the plutonium to Pu^{IV} so that a nitrous acid concentration of 0.05–0.1 M may arise at this stage. After air sparging this may fall to *ca.* 10^{-3} M HNO_2.

The increasing stability of oxidation state (III) with increasing atomic number in the transuranium elements results in the higher actinides, americium and curium, appearing in oxidation state (III) in the dissolver solution. The potential for the oxidation of Am^{3+} to AmO_2^{2+} in 1 M $HClO_4$ is reported[351] to be 1.69 V so that Am^{VI} is only formed under strongly oxidizing conditions. In aqueous bicarbonate solutions, AmO_2^{2+} is reduced rapidly[351] by nitrite to AmO_2^{+}. This ion in turn rapidly disproportionates[278,352] by a complicated mechanism, the overall effect of which is represented by equation (163). Rapid disproportionation of Am^{4+} also occurs[353] according to equation (164). Consequently the americium present in the dissolver solution will essentially all be converted to oxidation state (III). The stability constants for the complexation of Am^{3+} in media of unit ionic strength have been reported as $\beta_1 = 1.4$, $\beta_2 = 0.04$ for nitrate[354] at 26 °C and $\beta_1 = 9.11 \pm 0.56$ for nitrite[355] at 25 °C. The extraction of Am^{3+} from nitric acid solutions by TBP was shown[356] to involve the trisolvate $Am(NO_3)_3 \cdot 3TBP$, as found[357] for other trivalent actinides. The value of D_{Am} between 35% TBP in a hydrocarbon diluent and nitric acid was found[358] to increase with acidity to a maximum of *ca.* 0.03 between 2 and 3 M HNO_3 before falling off and then rising steeply again above 10 M HNO_3. The thermodynamics of Am^{3+} extraction from 2 M $LiNO_3$ at pH 2 by 0.25 M TBP in dodecane have been studied[359] and values of $\Delta H = -41.8$ kJ mol^{-1} and $\Delta S = -147.1$ J mol^{-1} K^{-1} obtained. Under Purex conditions the americium and curium, which behaves similarly, will thus pass with the FPs into the HAW stream from the decontamination cycle. Much higher D_{Am} values are obtained with acidic phosphorus ester extractants[360] so that the presence of HDBP from solvent degradation could impair decontamination from americium. However, the mass action effect of the UO_2^{2+} present is to remove any free HDBP so that americium retention in the solvent does not normally arise.

$$3AmO_2^{+} + 4H^{+} \rightleftharpoons 2AmO_2^{2+} + Am^{3+} + 2H_2O \quad (163)$$

$$2Am^{4+} + 2H_2O \rightleftharpoons Am^{3+} + AmO_2^{+} + 4H^{+} \quad (164)$$

$$PuO_2^{2+} + HNO_2 + 2H^{+} \rightarrow Pu^{4+} + HNO_3 + H_2O \quad (165)$$

$$3Pu^{4+} + 2H_2O \rightleftharpoons 2Pu^{3+} + PuO_2^{2+} + 4H^{+} \quad (166)$$

Plutonium is unusual among the actinides in that all four oxidation states from Pu^{III} to Pu^{VI} can coexist in aqueous solution. However, it is Pu^{4+} which predominates in the dissolver solution. The PuO_2^{2+} also present initially will be reduced by any nitrous acid[361] in the solution according to equation (165). Further conditioning of the dissolver solution with nitrogen oxides is sometimes used to ensure that all the plutonium is converted to Pu^{4+} before the first extraction cycle of the Purex process. Any Pu^{V} present would also be slowly reduced by HNO_2, but at acidities above 10^{-2} M, rapid disproportionation[278,279] of PuO_2^{+} occurs according to equation (155). At low acidities, disproportionation of Pu^{4+} may also occur. The overall process is described by equation (166), which implies a dependence upon $[H^+]^4$ for the equilibrium constant. A dependence on $[H^+]^{5.3}$ was reported for nitric acid media[362] and attributed in part to the effects of nitrate complexing. More recent studies[363] have indicated an equilibrium constant dependence on $[H^+]^{3.2}$ and $[NO_3]^{2.7}$. The thermal oxidation of Pu^{4+} to PuO_2^{2+} in 0.3 M HNO_3 has also been investigated[364] and appears to involve disproportionation followed by reoxidation of the Pu^{3+} formed to Pu^{4+}, the overall effect being a conversion of Pu^{4+} to PuO_2^{2+} which becomes significant at temperatures above 40 °C. The attainment of equilibrium in the disproportionation reaction is accelerated in the presence of UO_2^{2+} and a cation–cation complexation model was proposed[365] based on a stability constant of 0.8 ± 0.016 mol^{-1} for the formation of the $Pu^{IV} \cdot U^{VI}$ complex. The disproportionation of Pu^{4+} at ambient temperature is unlikely to require consideration in the Purex process unless acidities below *ca.* 0.5 M are anticipated. At lower acidities still, below *ca.* 0.1 M, the hydrolysis of Pu^{4+} to give a polymeric colloid may also occur.[366,367] The rate of polymer formation

was found to be third order in $[Pu^{IV}]$ and was retarded by $UO_2(NO_3)_2$.[367] The structure of the polymer remains uncertain although bridging hydroxy groups may be involved, as proposed[368] for the $\{Pu(\mu\text{-}OH)_2Pu\}^{6+}$ core in $Pu(OH)_2(SO_4)\cdot 4H_2O$ formed by thermal hydrolysis of $Pu(SO_4)_2$. Reactions such as these place a lower limit on the acidity acceptable for aqueous plutonium carrying streams in the Purex process. At nitric acid concentrations in excess of 10 M the Pu^{IV} is present[369] as $[Pu(NO_3)_6]^{2-}$, while at ionic strength 1.9 the stability constants for the formation of the lower nitrate complexes of Pu^{4+} have been reported[242] as $\beta_1 = 4.0$, $\beta_2 = 7.5$, $\beta_3 = 4.0$ and $\beta_4 = 1.2$. Typical aqueous phase acidities in the first extraction cycle of the Purex process might be between 1 and 3 M so that essentially all the plutonium would be present as Pu^{IV}.

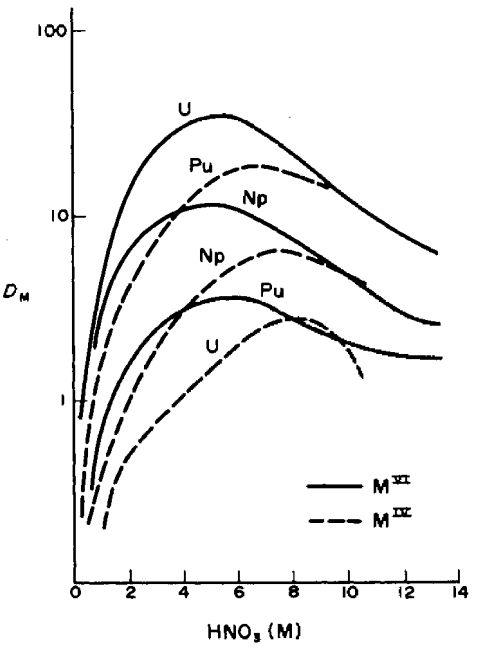


Figure 43 The extraction of actinides from HNO_3 by 19% TBP/OK[200,370]

The extraction of Pu^{4+} from nitric acid by TBP[272] involves the solvate $Pu(NO_3)_4\cdot 2TBP$ formed in a reaction stoichiometry analogous to that proposed[200] for Th^{4+} and shown in equation (167). The variation in $D_{Pu^{IV}}$ with HNO_3 concentration is shown in Figure 43 for extraction by 19% TBP/OK. This shows that Pu^{IV} is more extractable than U^{IV} or Np^{IV} but that Pu^{VI} is substantially less extractable than U^{VI}.[200,370] The thermodynamics of Pu^{IV} extraction have been investigated[371] and it was found that the unfavourable enthalpy term was offset by a positive entropy term arising from the dehydration of Pu^{4+} when forming $Pu(NO_3)_4\cdot 2TBP$. In the presence of U^{VI} the extraction of Pu^{IV} is suppressed,[372] as illustrated in Figure 44. However, $D_{Pu^{IV}}$ remains sufficiently high that essentially quantitative extraction is possible in the first cycle.

$$Pu^{4+}_{(aq)} + 4NO_3^-{}_{(aq)} + 2TBP_{(org)} \rightleftharpoons Pu(NO_3)_4\cdot 2TBP_{(org)} \qquad (167)$$

In order to effect a separation of uranium and plutonium it is necessary to adjust the plutonium oxidation state to (III), which is poorly extracted.[373] Provided the uranium remains as U^{VI} a partition is then possible with U^{VI} remaining in the organic phase while Pu^{III} passes into the aqueous phase. Contacting the Pu^{IV} and U^{VI} loaded solvent with an aqueous phase containing a suitable reducing agent will thus allow selective back extraction of the plutonium. The potential diagram[350] for plutonium at pH 0 is shown in Scheme 6. In the past, iron(II) sulfamate has been successfully used to effect this reduction. Unfortunately, this reagent is consumed in large excess over its stoichiometric requirement and contributes nonradioactive salts to the active waste streams. The reason for the nonstoichiometric behaviour and the choice of sulfamate as the anion lies in the fast autocatalytic reaction between Pu^{III} and nitrous acid,[374] which may be described[375] by equations (168)-(170). Nitrite oxidation of Fe^{2+} to Fe^{3+} may also occur according to equation (171). These reactions can result in the consumption of the reductant with little net change in plutonium oxidation state. To prevent this it is necessary to add a stabilizer which can remove

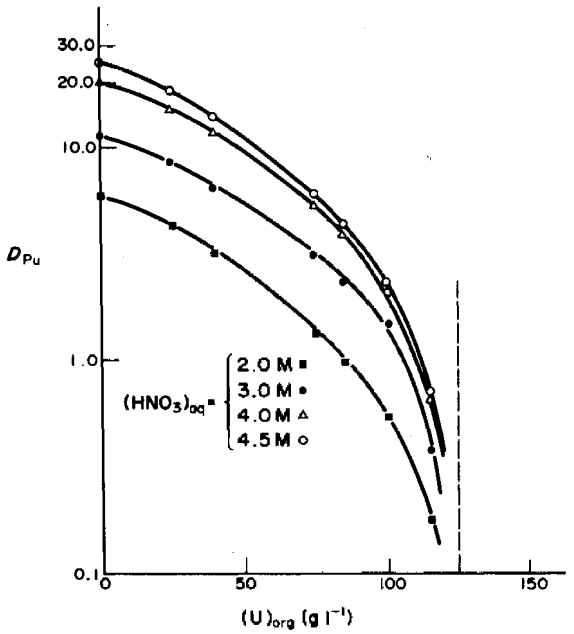


Figure 44 The variation in $D_{Pu^{IV}}$ between HNO_3 and 30% TBP/dodecane at 22 °C with increasing organic phase uranium concentration[372]

nitrous acid at a rate which competes with its autocatalytic generation in the Pu^{3+} oxidation reaction. The most suitable reagents for this are sulfamate, which reacts according to equation (172), and hydrazine, which reacts with excess nitrous acid according to equations (173) and (174).[376-378] Hydrazine has the clear advantage that its reaction products are gaseous and do not contribute to the process waste streams. However, the possibility that hydrazoic acid or metal azides may appear in the process streams must also be considered. Fortunately the azide complexing of actinide or lanthanide metals is weak compared with that of *d*-block metals.[379] Hydrazoic acid is also readily destroyed in nitric acid media by heating, the products of the reaction being N_2O, N_2 and NO.[380]

$$HNO_2 + HNO_3 \rightleftharpoons 2NO_2 + H_2O \quad (168)$$

$$Pu^{3+} + NO_2 \rightleftharpoons Pu^{4+} + NO_2^- \text{ (rate controlling)} \quad (169)$$

$$NO_2^- + H^+ \rightleftharpoons HNO_2 \quad (170)$$

$$Fe^{2+} + NO_2^- + 2H^+ \rightarrow Fe^{3+} + NO + H_2O \quad (171)$$

$$NH_2SO_3^- + NO_2^- \rightarrow N_2 + SO_4^{2-} + H_2O \quad (172)$$

$$N_2H_4 + HNO_2 \rightarrow HN_3 + 2H_2O \quad (173)$$

$$HN_3 + HNO_2 \rightarrow N_2O + N_2 + H_2O \quad (174)$$

Even in the presence of stabilizers, more than the stoichiometric quantities of reductant will be consumed. This largely results from the inextractability of $NH_2SO_3^-$ or hydrazine, present as $N_2H_5^+$. Nitric acid present in the organic phase reacts with traces of HNO_2, which is also readily extracted,[381] to produce NO_2 which can autocatalytically react with traces of Pu^{3+}. Since the stabilizer is not extracted the Pu^{III}-Pu^{IV} oxidation cycle can proceed unchecked in the organic phase, regenerating Pu^{IV}. This process is rapid at organic phase nitric acid concentrations of 0.2 M and above.[382] Consequently, an excess of reductant is necessary to maintain process control in the partition cycle. Stabilizers which are soluble in the organic phase might be used to reduce reductant consumption but those considered so far contribute organic products to the process

$$Pu^{III} \xrightarrow{0.98\ V} Pu^{IV} \xrightarrow{1.17\ V} Pu^{V} \xrightarrow{0.92\ V} Pu^{VI}$$

$$\xrightarrow{\qquad 1.04\ V \qquad}$$

Scheme 6

streams and offer an unacceptable alternative. Where hydrazine is used the effect on the distribution of Pu^{IV} and U^{VI} of salting by both the $N_2H_5 \cdot NO_3$ and the $Pu(NO_3)_3$ present in the aqueous phase may need to be considered.[383]

Alternatives to Fe^{II} as a reducing agent for Pu^{IV} are provided by U^{IV} and by hydroxyammonium nitrate (HAN).[384,385] In the case of HAN present in excess the dominant reduction reaction is represented by equation (175). However, where the Pu^{IV} concentration equals or exceeds the HAN concentration the reaction shown in equation (176) becomes important.[385] The rate of reduction was found to be inversely related to $[H^+]^4$ as shown by equation (177), where $k' = 0.029 \pm 0.008$ mol^5 s^{-1} and K_d, the dissociation constant for $\{Pu(NO_3)\}^{3+}$, $= 0.33 \pm 0.15$ mol at 30 °C. This rate becomes too slow to be acceptable at acidities above *ca.* 1 M so that HAN is not a suitable reductant for the first Purex cycle. However, its use in later cycles where lower acidities prevail may offer advantages since HAN is decomposed to N_2O by heating in nitric acid[287,288] and does not contribute to the HAW. This reaction involves both the oxidation of HAN by HNO_3 and its reaction with HNO_2, as shown in equations (178) and (179). Hydroxylamine also reduces Pu^{VI} in a mechanism involving reduction to Pu^{V}, which disproportionates to give Pu^{VI} and Pu^{III}. The Pu^{III} is then an effective reductant for Pu^{VI} and is itself converted to Pu^{IV} which is reduced by NH_2OH to regenerate Pu^{III} in an autocatalytic reaction sequence.[386] Other oximes have been found more effective than HAN for Pu^{IV} reduction,[387] but these contribute organic by-products to the process streams. A combination of HAN and iron(II) sulfamate is now used in the second cycle of the Purex process at the Savannah River Plant in the USA.[388]

$$2NH_3OH^+ + 2Pu^{4+} \rightarrow 2Pu^{3+} + N_2 + 2H_2O + 4H^+ \quad (175)$$

$$2NH_3OH^+ + 4Pu^{4+} \rightarrow 4Pu^{3+} + N_2O + H_2O + 6H^+ \quad (176)$$

$$-\frac{d[Pu^{IV}]}{dt} = k' \frac{[Pu^{IV}]^2[NH_3OH^+]^2}{[Pu^{III}]^2[H^+]^4(K_d + [NO_3^-])^2} \quad (177)$$

$$NH_3OH^+ + 2HNO_3 \rightarrow 3HNO_2 + H_3O^+ \quad (178)$$

$$NH_3OH^+ + HNO_2 \rightarrow N_2O + H_2O + H_3O^+ \quad (179)$$

Like Fe^{II}, U^{IV} reacts rapidly with Pu^{IV}.[389-391] The rate was found to vary inversely with $[H^+]^2$ and the reaction proceeded according to equation (180). A stabilizer is necessary to prevent the oxidation of U^{IV} by nitric or nitrous acid according to equations (181)-(183).[392] The oxidation

$$2Pu^{4+} + U^{4+} + 2H_2O \rightleftharpoons 2Pu^{3+} + UO_2^{2+} + 4H^+ \quad (180)$$

$$U^{4+} + NO_3^- + H_2O \rightarrow UO_2^{2+} + HNO_2 + H^+ \quad \text{(slow)} \quad (181)$$

$$U^{4+} + 2HNO_2 \rightarrow UO_2^{2+} + 2H^+ + 2NO \quad \text{(rapid)} \quad (182)$$

$$2NO + HNO_3 + H_2O \rightleftharpoons 3HNO_2 \quad \text{(rapid)} \quad (183)$$

by nitrate is favoured at low acidity while Pu^{III} oxidation is favoured at high acidity. The potential diagram for uranium oxidation states at pH 0 is given in Scheme 7. The U^{IV} may be generated

$$U^{III} \xrightarrow{-0.63\ V} U^{IV} \xrightarrow{0.61\ V} U^{V} \xrightarrow{0.063\ V} U^{IV}$$

$$\underbrace{\qquad\qquad 0.34\ V \qquad\qquad}$$

Scheme 7

externally and then fed into the process stream or it may be produced *in situ*, by electrochemical reduction. Photolytic production of U^{IV} has also been investigated[393] but, in the presence of hydrazine, photoexcited UO_2^{2+*} reacts to produce ammonia, which is an unacceptable by-product.[394] The reactions occurring during the *in situ* electrolysis are summarized[10,395] in equations (184)-(191). Both Pu^{IV} and U^{VI} are reduced at the cathode but U^{VI} reduction proceeds *via* U^{V}, which disproportionates according to equation (187). A polarographic study[396] of U^{VI} in TBP solution has shown that a one-electron reduction process may also occur in the organic phase. The reduction of Pu^{IV} by U^{IV} then proceeds according to equation (180). Nitric acid may also be reduced to nitrous acid according to equation (188), while any hydrazine present may be oxidized at the anode according to equation (189). Any neptunium present may also undergo reduction at the cathode according to equations (190) and (191). Atmospheric oxygen has been

found to oxidize U^{IV} in TBP/dodecane–HNO_3 mixtures.[397] In the organic phase the reaction was slow but could be accelerated by autocatalysis. A more rapid reaction occurred in the aqueous phase, which was zero order in $[U^{IV}]$, but both Pu^{III} and Fe^{II} were found to retard U^{IV} oxidation in mixed phase dispersions. Pilot scale trials have indicated that *in situ* electrolysis can produce U/Pu separation factors an order of magnitude higher than when reductive back extraction by solutions of U^{IV} is used.[10] In the latter case a five- to ten-fold excess of U^{IV} is required to obtain a separation factor of Pu from U of *ca.* 10^4.

$$Pu^{4+} + e^- \rightleftharpoons Pu^{3+}; \qquad E_0 = 0.92\ V \tag{184}$$

$$UO_2^{2+} + 4H^+ + 2e^- \rightleftharpoons U^{4+} + 2H_2O; \qquad E_0 = 0.33\ V \tag{185}$$

$$2UO_2^{2+} + 2e^- \rightleftharpoons 2UO_2^{+} \text{ (at the electrode)}; \qquad E_0 = 0.06\ V \tag{186}$$

$$2UO_2^{+} + 4H^+ + 4H_2O \rightleftharpoons UO_2^{2+} + U^{4+} + 6H_2O \tag{187}$$

$$NO_3^- + 3H^+ + 2e^- \rightleftharpoons HNO_2 + H_2O; \qquad E_0 = 0.94\ V \tag{188}$$

$$N_2H_5^+ \rightarrow N_2 + 5H^+ + 4e^-; \qquad E_0 = 0.23\ V \tag{189}$$

$$NpO_2^{2+} + e^- \rightleftharpoons NpO_2^{+}; \qquad E_0 = 1.15\ V \tag{190}$$

$$NpO_2^{+} + 4H^+ + e^- \rightleftharpoons Np^{4+} + 2H_2O; \qquad E_0 = 0.75\ V \tag{191}$$

The extraction of Pu^{3+} by TBP/OK resembles that of Am^{3+} in that the trisolvate $Pu(NO_3)_3 \cdot 3TBP$ is extracted[357,398] in a stoichiometry analogous to that shown for Ln^{3+} in equation (157). The value of $D_{Pu^{III}}$ for 19% TBP/OK–HNO_3 reaches a maximum of *ca.* 2×10^{-2} at 2 M HNO_3[373] so that effective back extraction of Pu^{III} from the organic phase is possible. Where U^{IV} is used as the reducing agent the uranium will be retained in the organic phase as $U(NO_3)_4 \cdot 2TBP$[399] and $UO_2(NO_3)_2 \cdot 2TBP$,[200,383] although $D_{U^{IV}}$ values[348] are lower than $D_{Pu^{IV}}$, as illustrated by Figure 43. The Pu^{III} may readily be reoxidized to Pu^{IV}, prior to extraction in subsequent purification cycles, by conditioning the solution with nitrogen oxides. The general coordination chemistry of plutonium in aqueous media has been reviewed by Cleveland[400] and the equilibrium constants for the plutonium oxidation states Pu^{IV}/Pu^{V}, Pu^{IV}/P^{VI} and Pu^{V}/Pu^{VI} have recently been re-evaluated,[401] good agreement with existing data being found.

Short-lived ^{239}Np is formed during the irradiation of ^{238}U containing fuels as shown in Scheme 1. The amount of ^{239}Np present will decline substantially during the cooling period between the discharge of the fuel from the reactor and its admission for reprocessing. However, the long-lived isotope ^{237}Np ($t_{1/2} = 1.7 \times 10^6$ y) is also formed and does not significantly decay during the cooling period. The presence of this isotope makes it desirable to divert neptunium into the HAW stream from the first Purex cycle, along with the FPs and americium. If uranium is to be recycled for enrichment it will be necessary to achieve DF_{Np} values of *ca.* 10^4. In nitric acid, neptunium is commonly encountered in oxidation states (IV), (V) and (VI). The aqueous coordination chemistry of neptunium has been reviewed in general[402] and, more specifically, in relation to the Purex process.[403] The redox potential diagram[350] for neptunium in 1 M $HClO_4$ is shown in Scheme 8 and the potential for the Np^{VI}/Np^{V} couple in 1.02 M HNO_3 was reported[242] to be 1.138 V. After fuel dissolution the neptunium is predominantly present in oxidation state (VI).[11] However, in the presence of nitrous acid, Np^{VI} will be reduced to Np^{V} according to equation (192), but at high acidity and low (less than 10^{-3} M) nitrous acid concentration, reoxidation of the NpO_2^+ by NO_3^- can occur.[10] Disproportionation of the NpO_2^+ is also possible according to equation (193),

$$2NpO_2^{2+} + HNO_2 + H_2O \rightleftharpoons 2NpO_2^{+} + 3H^+ + NO_3^- \tag{192}$$

$$2NpO_2^{+} + 4H^+ \rightleftharpoons Np^{4+} + NpO_2^{2+} + 2H_2O \tag{193}$$

although this is slow at low acidities. Thus NpO_2^+ is essentially stable in the range 0.1–2 M HNO_3 but above 6 M HNO_3 will be entirely converted to NpO_2^{2+} in a reaction catalyzed by traces of

$$Np^{III} \xrightarrow{0.16\ V} Np^{IV} \xrightarrow{0.74\ V} Np^{V} \xrightarrow{1.14\ V} Np^{VI}$$
$$\qquad\qquad\qquad

HNO_2.[10,404] In Purex feed solutions of less than 3.5 M HNO_3, over 89% of the neptunium was found to be Np^V, falling to *ca.* 85% in 4.8–5.3 M HNO_3. No Np^{VI} was found in the feed solution.[405]

The reduction of Np^V to Np^{IV} by a variety of reducing agents, including HAN,[406] hydrazine[407] and U^{IV},[408] has been investigated. At ambient temperatures the reduction by HAN or N_2H_4 was found to be slow but was accelerated by increased acidity or temperature.[407] At 61 °C and an ionic strength of 4 the rate of Np^V reduction was given by equation (194) where $k = (4.54 \pm 0.09) \times 10^{-2}$ $mol^{-2.65}$ min^{-1}. The reaction mechanism was complex but could be represented by equations (195)–(199). Rapid reduction of Np^{VI} by HAN was also observed according to equation (200) or, in the presence of excess Np^V, equation (201). The reduction of Np^V by hydrazine was found[406] to proceed according to equation (202) with the diimide N_2H_2 decomposing to give either $\frac{1}{2}N_2 + \frac{1}{2}N_2H_4$ or $\frac{1}{2}NH_3 + \frac{1}{2}HN_3$. The reaction was catalyzed by Fe^{III}, although Fe^{III} will itself oxidize Np^{IV} to Np^V. Oxidation of Np^{IV} by nitrate also occurs according to equation (203).[409] A five-step mechanism has been proposed[408] to describe the reduction of Np^V by U^{IV}, the overall reaction being represented by equation (204). The thermodynamic activation parameters for this reaction were evaluated as $\Delta G^* = 84 \pm 0.84$ kJ mol^{-1}, $\Delta H^* = 38 \pm 1.3$ kJ mol^{-1} and $\Delta S^* = 37 \pm 1.4$ J mol^{-1} K^{-1}. Weak cation–cation complex formation between Np^V and U^{VI} has been observed and is of an outer sphere nature.[410]

$$\frac{d[Np^V]}{dt} = k[Np^V][NH_3OH^+][H^+]^{1.65} \quad (194)$$

$$NpO_2H^{2+} + NH_3OH^+ \rightarrow Np(OH)^{3+} + NHOH + H_2O \quad \text{(slow)} \quad (195)$$

$$2NHOH \rightarrow N_2 + 2H_2O \quad \text{(fast)} \quad (196)$$

$$2NHOH + 2NpO_2H^{2+} \rightarrow H_2O + N_2O + 2Np(OH)_2^{2+} \quad \text{(fast)} \quad (197)$$

$$Np(OH)^{3+} + H^+ \rightarrow Np^{4+} + H_2O \quad \text{(fast)} \quad (198)$$

$$Np(OH)_2^{2+} + 2H^+ \rightarrow Np^{4+} + 2H_2O \quad \text{(fast)} \quad (199)$$

$$2NpO_2^{2+} + 2NH_3OH^+ \rightarrow 2NpO_2^+ + N_2 + 2H_2O + 4H^+ \quad (200)$$

$$4NpO_2^{2+} + 2NH_3OH^+ \rightarrow 4NpO_2^+ + N_2O + H_2O + 6H^+ \quad (201)$$

$$2NpO_2H^{2+} + N_2H_5^+ + 3H^+ \rightarrow 2Np^{4+} + N_2H_2 + 4H_2O \quad (202)$$

$$2Np^{4+} + NO_3^- + 3H_2O \rightarrow 2NpO_2^+ + HNO_2 + 5H^+ \quad (203)$$

$$U^{4+} + NpO_2^+ \rightleftharpoons UO_2^+ + Np^{4+} \quad (204)$$

The extraction of neptunium by TBP is highly oxidation state dependent. Thus Np^{IV} and Np^{VI} are extractable[347] and intermediate in behaviour between the corresponding uranium and plutonium species of the same oxidation state, as shown in Figure 43. The solvates $Np(NO_3)_4 \cdot 2TBP$[411] and $NpO_2(NO_3)_2 \cdot 2TBP$[412] are extracted in reactions analogous to those given for Pu^{IV} and U^{VI} in equations (167) and (110).[200] In contrast, Np^V is poorly extracted with D_{Np^V} for 30% TBP/OK and 1 M HNO_3 being 1.7×10^{-2} for a process which involves the monosolvate $NpO_2(NO_3) \cdot TBP$.[413] Thus careful control of the neptunium oxidation state is necessary to ensure an effective separation from Pu^{IV} and U^{VI}. Provided it is maintained in oxidation state (V), neptunium will pass into the aqueous raffinate of the first extraction cycle. However, control of the course of neptunium through the Purex process can sometimes present problems and in some cases conditions are arranged to allow the neptunium to pass through with the uranium before being removed in the uranium purification cycles.[11,414]

The chemistry of uranium in the Purex process is simpler than that of plutonium or neptunium. In the dissolver solution, U^{VI} is present exclusively. The lower oxidation states (IV) and (V) are both unstable in nitric acid media, U^V disproportionating rapidly and U^{IV} being formed only in the presence of medium strength reducing agents. In the absence of a stabilizer, U^{IV} is prone to oxidation by air and nitric or nitrous acid as discussed above. The extraction of U^{VI} by TBP[348] has been described in Section 65.2.3.1 and $D_{U^{VI}}$ values are larger than those of $D_{Pu^{VI}}$ or $D_{Np^{VI}}$ under comparable conditions, as shown in Figure 43. The presence of nitrous acid at concentrations in excess of 5×10^{-2} M has been found to suppress U^{VI} extraction[415] because of its competition for the TBP, as shown in equation (205). In its turn the U^{VI} present in the organic phase exerts a mass action effect on the FPs, present at much lower concentration, enhancing their retention in the aqueous raffinate of the first cycle.[10]

$$H^+_{(aq)} + NO_2^-{}_{(aq)} + TBP_{(org)} \rightleftharpoons HNO_2 \cdot TBP_{(org)} \quad (205)$$

Table 12 Thermodynamic Data for Actinide Extraction from 3 M Nitric Acid by 30% TBP/Xylene[416]

Actinide ion	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})
Th^{IV}	−8.11	−10.75	−8.83
U^{IV}	—	7.57	—
Np^{IV}	−11.71	10.50	74.5
Pu^{IV}	−18.70	6.02	82.8
U^{VI}	−11.50	−11.92	−1.44
Np^{VI}	—	−20.12	—
Pu^{VI}	—	−13.01	—

The enthalpy change for actinide extraction by TBP[416] is small and exothermic for An^{VI} but, with the exception of Th^{IV}, endothermic for An^{IV} as shown in Table 12. In the case of U^{VI} extraction from HNO_3 by TBP/dodecane the net enthalpy change was found[417] to be 20.9 ± 0.21 kJ mol^{-1}. The value of $D_{Pu^{IV}}$ was found to increase with temperature, reaching a maximum at 60 °C.[418] Measurements of the enthalpy of extraction of Pu^{IV} at low acidities are hampered by hydrolysis reactions but, generally, the enthalpies for actinide extraction by TBP appear to be rather insensitive to aqueous phase HNO_3 concentrations. The rates of transfer of Pu^{IV} and U^{VI} between phases were found to be rapid[213,348,419] and, in centrifugal contacters, mass transfer may be complete in 5–10 seconds.[420] The reductive back-extraction of Pu^{III} using Fe^{II} is also rapid in well-mixed two-phase systems, although the net mass transfer rate may be substantially reduced in the absence of effective stabilization to prevent reoxidation and reextraction of the plutonium.[421] Actinide retention in the organic phase during back extraction operations may result from the presence of acidic products from radiolytic solvent degradation. The distribution coefficients of H_2MBP and HDBP between nitric acid and TBP/OK are such that the bulk of the HDBP will be present in the organic phase while the H_2MBP will be largely in the aqueous phase.[10] The solubility of $Pu(NO_3)_2{\cdot}(DBP)_2$ in 10% TBP/hydrocarbon solutions is[422] *ca.* 10^{-3} M while $UO_2(DBP)_2$ is quite soluble.[10] In fact, $UO_2(DBP)_2$ itself is polymeric,[423] containing bridging DBP

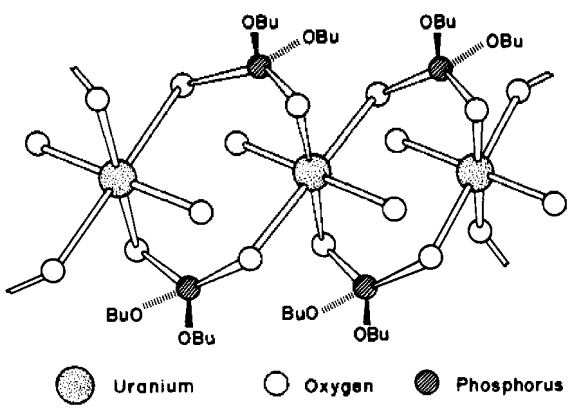


Figure 45 The structure of the $UO_2(DBP)_2$ polymer chain.[423] (Adapted from H. Burns, *Inorg. Chem.*, 1983, **22**, 1174, with permission from the American Chemical Society)

ligands and octahedrally coordinated uranium as shown in Figure 45. However, in the presence of tri-*n*-butylphosphine oxide (TBPO) a dimer of formula $[UO_2(NO_3)(DBP)(TBPO)]_2$ is formed,[423] as shown in Figure 46. This may represent the species which is soluble in TBP but having TBPO in place of TBP. The suppression of polymer formation by adduct formation of this type may also account for the synergistic effect of certain neutral ligands on UO_2^{2+} extraction by dialkyl phosphates referred to in Section 65.2.2.1(iv). High organic phase uranium loadings can thus remove DBP and suppress $Zr(OH)(NO_3)(DBP)_2$ precipitation. However, the formation of Zr^{IV} precipitates is, in any case, slow and retarded by high HNO_3 concentrations. Phosphoric acid itself forms highly insoluble precipitates with Zr^{IV} but only modestly suppresses Pu^{IV} extraction.[207] The solubility products of $UO_2(HPO_4)$ and $(UO_2)_3(PO_4)_2$ have been evaluated as 10^{-12} and 10^{-50} respectively.[424] Any hydroxamic acids which might result from radiolytic degradation of the diluent in the presence[10] of HNO_3 would be effective complexing agents for U^{VI} or Zr^{IV}.[325] However, they would also be readily destroyed by any nitrous acid present and have not

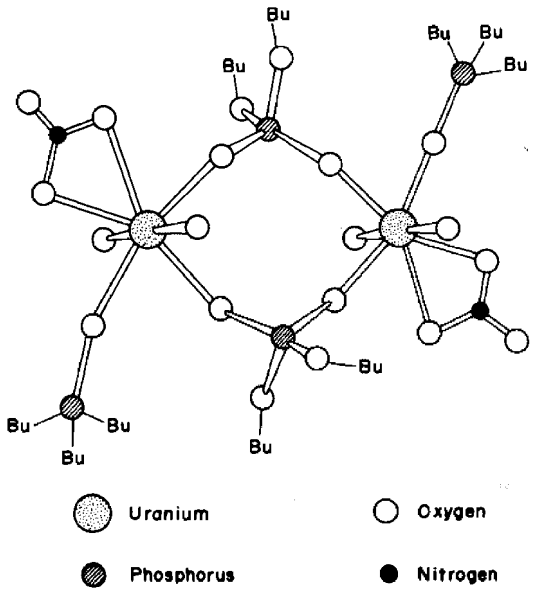


Figure 46 The structure of $[UO_2(DBP)(TBPO)(NO_3)]_2$.[423] (Adapted from H. Burns, *Inorg. Chem.*, 1983, **22**, 1174, with permission from the American Chemical Society)

in fact been detected in Purex process streams.[290] Scrubbing the recycled solvent with solutions of sodium carbonate is effective in removing HDBP and its complexes so that DF_{Ru} and DF_{Zr} values of *ca.* 100 may be obtained after a 5 minute contact.[425] Hydrazine carbonate has been proposed as a 'salt free' reductive scrub for TBP.[425] Allowing the solvent to age prior to scrubbing is highly detrimental to the effectiveness of carbonate treatments and greatly increases the contact times needed.[426]

Many different Purex flowsheets have been proposed and investigated. Those which are used in commercial plants will be tailored to suit the particular process requirements of the plant.[9,427] However, some general features relating to the choice of flowsheet conditions are noteworthy.[10] A high uranium loading in the first cycle is desirable to optimize FP decontamination. In practice, 80% saturation of 30% TBP/OK by uranium is the maximum which can be tolerated before the density difference between the phases becomes unacceptably small.[10] High acidity, 2–4 M HNO_3, suppresses the formation of interfacial precipitates of Zr^{IV}-alkyl phosphoric acid complexes and suppresses ruthenium extraction, while lower acidities, 1.5 M HNO_3, offer better zirconium decontamination. Consequently a dual scrub with 4 M HNO_3 followed by 1.5 M HNO_3 has been proposed for the first cycle.[286] Dual temperature scrubs have also been recommended, with Zr^{IV} being removed at 30 °C after which a 70 °C scrub more effectively removes ruthenium. The decontamination factors achieved will also depend on the type of equipment used. Mixer settlers give longer contact times, greater solvent radiolysis, and thus lower $DF_{Zr/Nb}$ values than pulsed columns, which lead to an order of magnitude less HDBP production. Centrifugal contactors offer a further improvement but at the expense of greater mechanical complexity in the highly active section of the plant.[10] Some typical *DF* values attained by the Purex process are given in Table 13.

After the U/Pu partition stage the uranium loaded organic phase may be back extracted with water or dilute nitric acid to give an aqueous uranium stream which passes to further purification

Table 13 Typical Decontamination Factors Attained by the Purex Process[285]

	Plutonium product			*Uranium product*		
DF for	*Total γ*	*Zr + Nb*	*Ru*	*Total γ*	*Zr + Nb*	*Ru*
One cycle	2×10^3	3×10^3	10^3	5×10^3	3×10^3	2×10^3
Two cycles	2×10^6	6×10^6	10^5	4×10^5	5×10^6	3×10^5

cycles of solvent extraction. A reductive scrub of the organic uranium stream may then be used to remove residual plutonium while scrubbing with $>10^{-2}$ M HNO_2 will remove Np^V. The aqueous plutonium stream from the partition cycle may be reoxidized using nitrogen oxides prior to passing to additional purification cycles. In the $Pu(NO_3)_4$–HNO_3–H_2O–TBP–OK system a third phase containing 185 g dm^{-3} Pu^{IV} can form when Pu^{IV} loadings exceed 40 g dm^{-3} in 30% TBP/OK.[428] This limits the acceptable organic phase actinide content and gives lower FP decontamination factors than are achieved in the first cycle with U^{VI} present. Back extraction of Pu^{IV} with dilute nitric acid gives rise to a rather dilute aqueous product stream and electroreduction or back extraction with HAN[429] may be used to obtain product streams containing *ca.* 60 g dm^{-3} plutonium.[10] Alternatively, the complexation of Pu^{IV} by aqueous sulfate[430] may be used. The solution produced will be suitable for oxalate precipitation processes but will give rise to a sulfate bearing waste stream. Because of the security issues associated with plutonium production, Purex flowsheets are now also subject to design parameters which relate to the control of fissile material inventories to avoid diversion into weapons production.[431]

Operational experience of the application of the Purex process to oxide fuel reprocessing has been reviewed by Hine,[432] and technologies for reprocessing nuclear fuels have been surveyed.[433] The use of higher levels of power reactor fuel irradiation and the introduction of breeder reactors will lead to increased solvent radiation doses in the first cycle of the Purex process. Improvements in the process which limit solvent radiolysis effects are thus of particular importance for the future. One strategy, described by McKibben,[338] is the so called 'permanganate strike'. This involves the addition of externally produced MnO_2 to the dissolver solution, or its *in situ* production from the addition of $KMnO_4$ and $Mn(NO_3)_2$. The MnO_2 acts as an adsorbent for zirconium and niobium but not for Ce^{3+}, Am^{3+}, UO_2^{2+} or Pu^{4+} ions. Separation of the solid MnO_2 from the dissolver solution prior to the first cycle of solvent extraction thus substantially reduces the radiation dose to the solvent. The carry over of zirconium and niobium into subsequent process cycles is also substantially reduced so that shorter cooling periods may be used, even for highly irradiated fuel. The Purex process is now so well tried and established that it is difficult to conceive of its being replaced by any alternative method of reprocessing reactor fuels during the foreseeable future. However, improvements and alternatives continue to be proposed and investigated. McKay has considered[245] the possible application of other solvent systems to LMFBR fuel reprocessing. He concluded that TBP would not be superseded as the extractant of choice in the short term, but that reagents such as dibutyl phosphonate (DBBP) might have potential for use in flowsheets using low extractant concentrations. These give high FP rejection in the first cycle at the expense of a reduced solvent capacity for carrying actinides. Extractants of higher capacity, such as DBBP, would thus be better suited for use in such flowsheets. Ether diluents, such as dibutyl ether, might also have advantages over OK since their radiolysis products would be less detrimental to process performance.

(iv) Breeder reactor fuels

There are two breeder reactor fuel cycles. One involves the irradiation of $^{238}U/^{239}Pu$ oxide fuel with fast neutrons and is at the prototype stage of development. The other involves the irradiation of $^{232}Th/^{233}U$ oxide fuel with thermal neutrons and is at the experimental stage. Fuel from the $^{238}U/^{239}Pu$ cycle may be reprocessed using Purex technology adapted to accommodate the significant proportion of plutonium present in the fuel. Increased americium and neptunium levels will also arise compared with thermal reactor fuel. The $^{232}Th/^{233}U$ fuel may also be reprocessed using solvent extraction with TBP in the Thorex (Thorium Recovery by Extraction) process. In this case the extraction chemistry must also take account of the presence of ^{233}Pa arising as shown in Scheme 2.

Plants in the UK, USSR and France are now reprocessing irradiated UO_2/PuO_2 fuels and LMFBR fuel reprocessing has been the subject of international conferences.[15,434] The plant at Cap la Hague, France, employs a 30% TBP solution and no U/Pu separation is undertaken, so that a mixed U/Pu product is obtained. Fluoride is added to the process feed to complex zirconium and suppress its extraction.[435] The Dounreay plant in the UK employs a 20% TBP/OK solution and uses sulfuric acid to effect the U/Pu separation.[436] TBP poorly extracts Pu^{IV} or U^{VI} from sulfuric acid solutions, but in mixed HNO_3/H_2SO_4 the equilibria shown in equations (206) and (207) must be considered. The equilibrium constants for these reactions, K_P and K_U, are given

$$Pu(NO_3)_4 + 2H_2SO_4 \rightleftharpoons Pu(SO_4)_2 + 4HNO_3 \quad (206)$$

$$UO_2(NO_3)_2 + H_2SO_4 \rightleftharpoons UO_2(SO_4) + 2HNO_3 \quad (207)$$

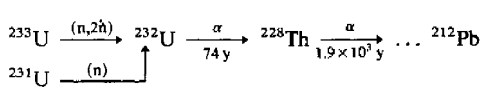
by equations (208) and (209) where $[A]=[HNO_3]^2/[H_2SO_4]$ and $K_P \gg K_U$. The formation constants for $Pu(SO_4)^{2+}$, $Pu(NO_3)(SO_4)^+$ and $Pu(SO_4)_2$ have been reported as $\beta = 6.9\times10^2$, 1.08×10^3 and 5.1×10^4 respectively on the basis of solvent extraction experiments.[437] Thermodynamic data for the formation of uranyl sulfate complexes are given in Table 7. Neptunium[438] and americium[439]

$$K_P = \frac{[Pu(SO_4)_2][A]^2}{[Pu(NO_3)_4]} \tag{208}$$

$$K_U = \frac{[UO_2(SO_4)][A]}{[UO_2(NO_3)_2]} \tag{209}$$

also form sulfate complexes but in the cases of Np^V and Am^{III} these are charged and inextractable. Adjusting the value of [A] provides a means of separating Pu^{IV} and U^{IV}. Because $K_P \gg K_U$ and K_P is related to $[A]^2$, conditions can be defined under which Pu^{IV} passes to the aqueous phase while leaving U^{VI} in the organic phase.[435] The Pu^{IV} may be re-extracted by increasing [A]. Although this means of effecting the U/Pu split contributes sulfate to the process waste streams, it avoids the need for a reducing agent. The higher plutonium content of LMFBR fuel would require the use of unacceptably large volumes of iron(II) sulfamate in a reductive back-extraction of plutonium. HAN is also unsuitable because of the slow kinetics of its reaction with Pu^{IV}. An outline flowsheet for Prototype Fast Reactor (PFR) fuel reprocessing at Dounreay is illustrated in Figure 47. In the first cycle a partial separation of U^{VI} from Pu^{IV} is made. In practice, U^{VI} is found to prevent third-phase formation so that higher solvent loadings are possible than with Pu^{IV} alone. Although a pure $Pu(NO_3)_4$ product stream is ultimately produced by this flowsheet, it would be possible to produce a mixed U/Pu product stream. After blending to adjust the U/Pu ratio this might be used directly in the Sol-Gel process to produce UO_2/PuO_2 fuel. Such an approach has the advantage, in terms of security, that at no stage in the process is a stream containing entirely fissile actinides produced.

Irradiated ThO_2/UO_2 breeder fuels may also be reprocessed using solvent extraction with TBP in the Thorex process.[285,349] The $^{232}Th/^{233}U$ fuel cycle presents several additional challenges to the fuel reprocessor. The ^{233}Pa precursor of ^{233}U has a substantially longer half-life than ^{239}Np in the $^{238}U/^{239}Pu$ cycle. Thus, unless very long fuel cooling times were allowed prior to reprocessing, there would be substantial quantities of highly active ^{233}Pa in the process feed. Most of this would pass to the HAW in the first Thorex cycle, and would lead to loss of ^{233}U from the fuel cycle unless a separate process for ^{233}Pa or ^{233}U recovery from the HAW were used. A more serious problem would arise from the formation of ^{232}U by neutron capture and its decay to ^{228}Th, as shown in Scheme 9. The short half-lives of these isotopes, and of some ^{228}Th daughters, make them intensely radioactive. No matter what process strategy were used they would accumulate in the $^{232}Th/^{233}U$ fuel cycle and necessitate remote handling at all stages. Also, in combination with the ^{233}Pa present, they would give rise to high solvent radiation doses and increased TBP and diluent degradation compared with Purex experience. Chemical difficulties might then arise from the increased formation of HDBP, which can form insoluble complexes with Th^{IV}.[285] Other chemical problems arise from the possibility of third-phase formation during TBP extraction of Th^{IV} and from the low solubility of ThO_2 in nitric acid. Addition of fluoride ion to the dissolver solution allows ThO_2 dissolution but contributes an additional, and potentially complexing, anion to the first cycle aqueous feed. The extraction chemistry of Pa^V also differs from that of Np^V so that new complications arise from the presence of ^{233}Pa.



Scheme 9

Irradiated ThO_2/UO_2 fuel can be dissolved in the Thorex reagent consisting of 13 M HNO_3, 0.05 M HF and 0.1 M $Al(NO_3)_3$. This gives rise to a solution containing Th^{IV}, U^{VI} and Pa^V. The solution chemistry of protactinium has been reviewed[92,440] and, although Pa^{IV} is stable in aqueous media, it is readily oxidized by air so that only Pa^V would arise in the dissolver solution. In nitric acid media, Pa^V forms complexes of the general formula $Pa(OH)_x(NO_3)_y^z$ where $(x, y, z) =$ (3, 1, +1), (2, 1, +2) and (2, 2, +1) in 1-2 M HNO_3, (2, 3, 0), (2, 4, −1) and (1, 3, +1) in 2-6 M HNO_3 and (2, 3, 0) and (2, 4, −1) in 6-12 M HNO_3.[441] Some equilibrium constants[440,442] for the formation of such complexes in media of ionic strength 5 M are shown in Table 14. Only the

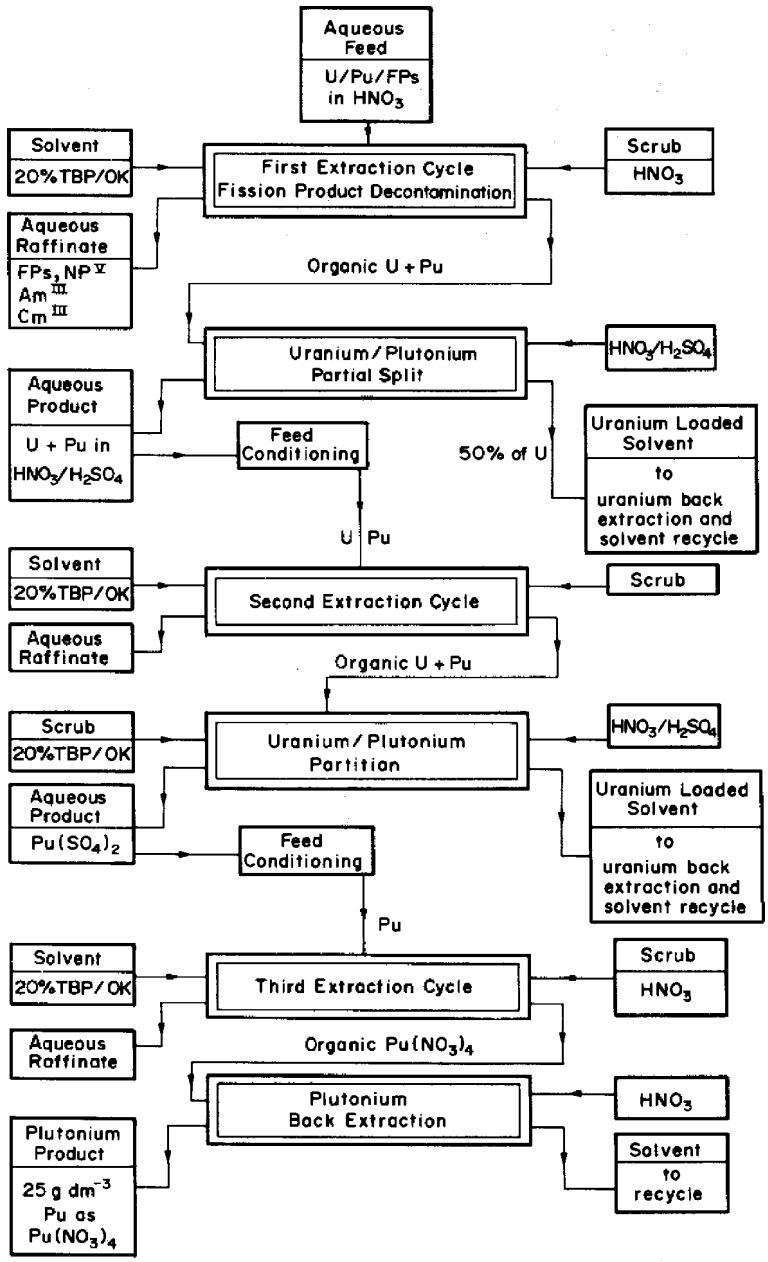


Figure 47 An outline flowsheet for the reprocessing of Prototype Fast Reactor fuel at Dounreay[436]

Table 14 Equilibrium Constants[441] for Nitrate Complexes of Pa^{V}

Species	*Equilibrium expression*	*log K*[a]
$Pa(OH)_2(NO_3)^{2+}$	$\frac{[Pa(OH)_2(NO_3)^{2+}]}{[Pa(OH)_2^{2+}][NO_3^-]}$	1.23
$Pa(OH)_2(NO_3)_2^+$	$\frac{[Pa(OH)_2(NO_3)_2^+]}{[Pa(OH)_2^{3+}][NO_3]^2}$	2.11
$Pa(OH)_2(NO_3)_3$	$\frac{[Pa(OH)_2(NO_3)_3]}{[Pa(OH)_2^{3+}][NO_3^-]^3}$	2.73
$Pa(OH)_2(NO_3)_4^-$	$\frac{[Pa(OH)_2(NO_3)_4^-]}{[Pa(OH)_2^{3+}][NO_3^-]^4}$	3.15

[a] In 5 M ($Li^+/Na^+/H^+ClO_4^-/NO_3^-$) medium.

(2, 3, 0) complex was found to be extracted by TBP, forming the disolvate $Pa(OH)_2(NO_3)_3 \cdot 2TBP$. The value of D_{Pa^V} between 30% TBP/OK and HNO_3 was found to increase rapidly from <0.1 below 1 M HNO_3 to almost 2 at 4 M HNO_3. The value then increased further with increasing acidity to reach $D_{Pa^V} = 10$ at 12 M HNO_3. At lower acidities this behaviour reflects the increasing proportion of the neutral (2, 3, 0) complex present as the acidity increases. Other workers have reported[443] the extraction of $Pa(NO_3)_5 \cdot 2TBP$ from 3 M HNO_3 by TBP. However, only compounds of formula $PaO(NO_3)_3 \cdot xH_2O$, where $x = 1.5$–4.0, have been isolated[444] from fuming nitric acid solutions of Pa^V. Simple complexes of Pa^{5+} such as $HPa(NO_3)_6$ were only isolated under anhydrous conditions. The extraction of U^{VI} and Th^{IV} by TBP has been described in Sections 65.2.3.1 and 65.2.3.2 respectively. The value of D_{Th} is suppressed by increasing U^{VI} concentrations, as shown in Figure 48.

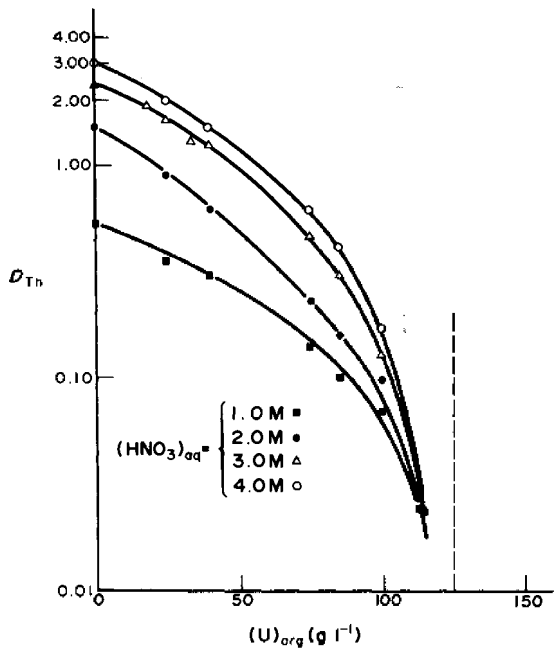


Figure 48 The variation in $D_{Th^{IV}}$ between nitric acid and 30% TBP/dodecane at 22 °C with increasing organic phase uranium concentration[372]

In an early Thorex flowsheet, three different solvent systems were used. Firstly, diisobutyl carbinol, $C_4H_9OCH_2CH_2OCH_2CH_2OC_4H_9$, was used to extract ^{233}Pa and reduce the radiation dose to the solvent in subsequent cycles.[445] The uranium was next extracted using 5% TBP in Amsco (a hydrocarbon diluent) and finally the thorium was extracted using 45% TBP plus 15% benzene in Amsco, to leave the FPs in the aqueous raffinate. The complexities of operating with three solvents led to this flowsheet being superseded by processes using only TBP. An example of such a flowsheet is shown in outline in Figure 49; this used 43.5% TBP/Amsco as the solvent.[9,285] Some salting with $Al(NO_3)_3$ was used in the first cycle in which U^{VI} and Th^{IV} are extracted together from an acid-deficient aqueous phase. The aluminum also served to complex fluoride ions and prevent the formation of thorium fluoride complexes which would affect thorium extraction. The U/Th mixture was then back extracted with $Al(NO_3)_3$ solution and its composition adjusted by evaporation before being fed to a second solvent extraction cycle. The thorium was then selectively back extracted from the organic phase under carefully controlled conditions using dilute HNO_3 to give the aqueous thorium product. The uranium was subsequently back extracted using water. Examples of the decontamination factors attained with this flowsheet are given in Table 15 and ruthenium emerges as the most problematic fission product.

More recently a flowsheet has been developed which employs 30% TBP/OK as the solvent.[349,446,447] This involves the use of an acid feed to the first cycle to assist in zirconium decontamination and suppress hydrolysis. An acid-deficient partition cycle then follows in which the U-Th separation is effected. A pilot plant (JUPITER) has been constructed at Julich in Germany to process ThO_2/UO_2 fuel using this flowsheet. Although a complete separation of thorium, uranium and FPs is possible using TBP in the Thorex process,[448] alternative approaches

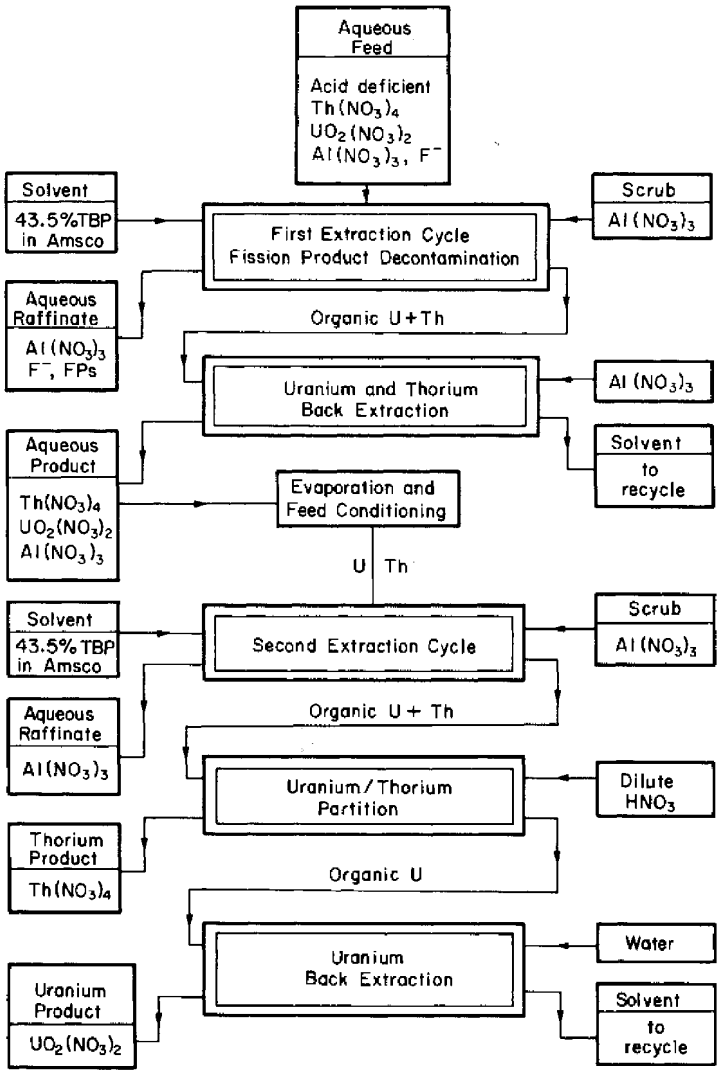


Figure 49 An outline flowsheet for the Thorex process

continue to be investigated. The extraction of Th^{4+} by trialkyl phosphates has been found[192] to vary with the steric bulk of the alkyl groups while that of UO_2^{2+} is much less variable. This was attributed to an entropy effect which was more pronounced for $Th(NO_3)_4$, which forms a trisolvate, than for $UO_2(NO_3)_2$, which forms a disolvate. Careful choice of the alkyl groups might thus allow improvements in the selectivity of extractants for Th/U processing.[449] Increased organic phase loadings have been possible using a dual extractant system involving dipentyl pentylphosphonate in dodecane and tricaprylammonium nitrate in Arom 100.[450] Uranium is back extracted with nitric acid and thorium with formic acid. The use of the tertiary amine extractant improves solvent

Table 15 Decontamination Factors in the Thorex Process[285]

	Decontamination factors					
Cooling period	*30 days*		*250 days*		*400 days*	
Process cycles	*One*		*One*		*Two*	
Contaminant	*Th*	*U*	*Th*	*U*	*Th*	*U*
Gross γ	400	4×10^4	3×10^3	3×10^4	5×10^4	3×10^5
Pa γ	1×10^4	1×10^6	3×10^3	2×10^5	2×10^4	2×10^5
Ru γ	2	300	580	4×10^3	2×10^4	1×10^5
Zr-Nb γ	1×10^3	5×10^4	3×10^3	5×10^4	7×10^4	3×10^5
Total Rare Earth β	1×10^3	3×10^7	2×10^5	2×10^7	1×10^6	1×10^7

viscosity and avoids the problem of third-phase formation. However, past experience suggests that multiextractant processes are unlikely to gain acceptance for commercial reprocessing of power reactor fuels.

65.2.4.4 Waste treatment and the recovery of radionuclides

Radionuclides for commercial or experimental use are usually produced by the irradiation of specially prepared target materials. Their recovery from power reactor fuel waste has not been common practice, although a process for the large-scale recovery of FPs has been described.[451] In recent times the increasing quantities of HAW arising, and the need to minimize the volume of material destined for very long-term storage, has encouraged the development of processes to separate the longer lived nuclides from the bulk of the HAW. Since these processes are not yet well established, they offer some scope for innovation and the use of new types of reagent. In one such example a cyclic polyether, dibenzo-21-crown-7, has been shown to extract Cs^+ selectively from medium active waste solutions. Using $SbCl_6^-$ or phosphomolybdate as the counter ion, high selectivity and D_{Cs} values between 10 and 100 were obtained.[452] A wide variety of techniques has been applied to the separation of particular isotopes. In one example of a laboratory separation of the components of an irradiated fuel sample for analytical purposes, solvent extraction, ion exchange, partition chromatography and simple precipitation methods were all used.[453] More recent examples of processes for separating specific actinides have been described at international conferences[8,12] and the applications of solvent extraction[5,9] and ion exchange[8,454,455] methods have been reviewed. Among the FPs, only ^{99}Tc has a sufficiently long half-life (2.12×10^5 y) to warrant separation on waste management grounds.

At the Hanford plant in the USA, ^{90}Sr, ^{144}Ce and ^{147}Pm have been recovered because of their potential for use in heat sources, while ^{137}Cs was recovered for use as a γ-ray source.[451] The ^{137}Cs could be separated from aged Purex waste by ion exchange on aluminosilicate or precipitation with phosphotungstic acid. Strontium and the lanthanide ions could be precipitated in a lead sulfate carrier matrix, redissolved and the lanthanides precipitated with oxalate. The strontium solution could then be further purified by solvent extraction with HDEHP/TBP mixtures, in the presence of diethylenetriaminepentaacetic acid (DTPA) to suppress the extraction of contaminants. The strontium was next back-extracted using citrate solution and the citrate complex finally converted to $Sr(NO_3)_2$ by treatment with H_2O_2 in nitric acid. The cerium and promethium were separated in a solvent extraction process using HDEHP after conditioning with *N*-hydroxyethylenediaminetriacetic acid to suppress lead extraction. Back extraction of the lanthanides into nitric acid containing sodium persulfate provided an aqueous phase containing Ln^{3+} with the cerium remaining in the organic phase as Ce^{4+}. Further solvent extraction purification of the Ln^{3+} stream followed by ion exchange chromatography and elution with DTPA afforded a purified promethium product. The cerium was recovered by reductive back extraction with nitric acid containing nitrite to give an aqueous $Ce(NO_3)_3$ product stream. The complex nature of this separation process illustrates the difficulties of fractionating the HAW from power reactor fuel processing into pure products. The problem is simplified somewhat if pure products are not required and groups of chemically related isotopes, such as the oxidation state (III) actinides, are to be removed for waste management purposes.

The separations of the transplutonium elements and the lanthanides have been extensively studied in the development of processes to produce samples of the heavier actinides for laboratory study. Examples of such processes include Talspeak[456] (Trivalent actinide and lanthanide separation by phosphorus-reagent extraction from aqueous complexes), Tramex[457] (Tertiary amine extraction) and Cleanex.[458] The selection of extractants for effecting actinide separations[449,459] and the potential of extractants containing nitrogen or sulfur donor atoms[460] have also been reviewed. Chelating extractants such as the carbamoyl methylphosphonates,[461] $(RO)_2P(O)CH_2C(O)NR'_2$, or the bifunctional systems $R_2P(O)CH_2C(O)NR_2$[462] and $\{R_2P(O)\}_2X$,[463] where R = alkyl or aryl, R′ = alkyl and X is an alkyl, alkenyl or aryl bridging group, have shown promise as reagents for extracting trivalent ions. The structures of the chelate rings, and the basicity of the oxygen donor groups, both affect extractant performance. In the case of $\{Ph_2P(O)\}_2X$, for example, $D_{An^{III}}$ decreased by *ca.* 10^3 as X was varied from $-CH_2-$ to $-CH_2CH_2-$ but was little changed when X was varied from $-CH_2-$ to $-CH{=}CH-$.[463] Dihexyl *N,N*-diethylcarbamoylmethylenephosphonate (DHDECMP) has been used to extract trivalent ions from HAW.[456] After back extraction with nitric acid or carbonate solution the lanthanides

and actinides were separated by the Talspeak process. This involved coextraction by HDEHP from an acidic aqueous phase containing acetate and nitrate. The trivalent actinides were then back extracted using aqueous DTPA/acetate solution. The complexation of actinide ions by carboxylic acids and amine carboxylic acids has been reviewed.[464] Acidification of this aqueous stream followed by a further cycle of HDEHP extraction and nitric acid back extraction afforded an aqueous product containing $Am(NO_3)_3$ and $Cm(NO_3)_3$. In dimerizing diluents the extraction of Am^{3+} by HDEHP may be represented[111] by equation (210), but in the monomerizing solvent 2-ethylhexanoic acid (HEHA) the extracted species was found to be $Am\{DEHP{\cdot}HEHA\}_3$.[465] An alternative means of separating An^{3+} and Ln^{3+} has been proposed[466] based on the solvent extraction removal of the later lanthanides by HDEHP. This is followed by the extraction of Am^{3+} and Cm^{3+} using a derivative of 8-hydroxyquinoline to separate these actinides from the early lanthanides. Such a process would operate on dilute aqueous mineral acid solutions and would not require reagents such as DTPA to effect the partition of An^{3+} and Ln^{3+}.

$$Am^{3+}_{(aq)} + 6HDEHP_{(org)} \rightleftharpoons Am\{(DEHP)_2H\}_{3(org)} + 3H^+_{(aq)} \quad (210)$$

The Cleanex process[458] was adapted from the DAPEX process described in Section 65.2.2.1(iv) and also utilizes HDEHP to coextract the lanthanides and transplutonium elements. Subsequent separation of these two groups may then be carried out using, for example, the Tramex process.[457] This involves the use of tertiary amine extraction of the An^{3+} ions from acidic 11 M LiCl solutions. Spectroscopic studies[467] have indicated that, in the cases of Am^{3+} and Nd^{3+} at least, the octahedral trianionic hexachloro complexes are extracted from 11 M LiCl. Stability constant data for the chloride complexing of Am^{3+}, Cm^{3+} and Cf^{3+} in media of ionic strength 1.0 have been reported.[468] Tertiary amines[469] also extract Pu^{IV} and a study of extraction from nitrate media by trilaurylamine (TLA) in xylene has been reported.[470] This showed that the mass transfer rate was controlled by the reactions between Pu^{IV} from the bulk phase and interfacially adsorbed $TLA{\cdot}HNO_3$. The separation of individual transplutonium elements from the Tramex actinide product may be achieved using ion exchange or precipitation techniques.[471]

Liljenzin and coworkers have described the CTH process for separating both actinides and technetium from HAW using solvent extraction.[472] The process development was based upon comprehensive studies of the distribution data of FPs and actinides between nitric acid media and 50% TBP[473] or 1 M HDEHP[474] in an aliphatic diluent. These allowed empirical equations to be developed for use in the process design. Three consecutive solvent extraction cycles were used. In the first, uranium, neptunium and plutonium were recovered from 6 M HNO_3 by extraction with 1 M HDEHP. In the second cycle, extraction with 50% TBP/OK was used to reduce the aqueous phase acidity to 0.1 M HNO_3. The technetium and some ruthenium and palladium were also removed in this cycle. Finally the lanthanides and trivalent actinides (Am and Cm) were extracted in a third cycle using 1 M HDEHP again. The remaining fission products could then be removed by sorption on to ion exchange media to give a decontaminated aqueous waste stream. The lighter actinides from the first cycle could be returned to the Purex process after purification, while the lanthanides and transplutonium elements from the third cycle could be separated using the Talspeak process. Hot tests of the CTH process established that it largely performed according to expectation. Losses of uranium and plutonium were below 0.1% and of americium and curium below 0.2%. Recoveries of better than 99.8% for neptunium and 97% for technetium were also achieved. Decontamination factors of over 10^5 for α-activity were achieved by the solvent extraction section, while the ion exchangers gave over 3×10^4 as the decontamination factor on β-activity. The residual activity in the process waste was dominated by ^{125}Sb. The CTH process was thought to be entirely compatible with Purex operations and suitable for full scale implementation.

In addition to the aqueous raffinates from the solvent extraction cycles of the Purex process, an actinide bearing waste stream will arise from the washing of the TBP/OK solvent prior to its recycle to the first cycle. These wastes will typically contain actinides in a mixed $Na_2CO_3/NaNO_3$ solution which also contains H_2MBP and HDBP. The uranium present will form soluble U^{VI} complexes with carbonate, as discussed in Section 65.2.2.1(i). Carbonate complexation of Pu^{IV} also leads to solubility in alkaline solutions and in Na_2CO_3 media precipitation did not occur below pH 11.4,[475] although precipitates did form on reduction to Pu^{III}. One Pu^{III} species precipitated from carbonate media has been identified[476] as $Pu(OH)_3{\cdot}Pu_2(CO_3)_3{\cdot}H_2O$. In 2 M Na_2CO_3 media, Np^{IV} is oxidized by air to Np^{V} above pH 11.7 while Np^{VI} either precipitates or is reduced above pH 13.[477] The potential of the Am^{IV}/Am^{III} couple, in common with those of other actinides, becomes more cathodic with increasing carbonate concentration.[478] In the total bicarbonate plus carbonate concentration range 1.2–2.3 M all the americium oxidation states from (III) to (VI)

can coexist in equilibrium. Carbonate complexing of Am^{III} was found to be stronger than that of nitrate[479] and at low carbonate concentrations (0.12–0.6 M) the principal species in solution was found to be $[Am(OH)(CO_3)_3]^{4-}$.

The recovery of actinides from such solutions by acidification with HNO_3 followed by solvent extraction is hampered by the accumulation of H_2MBP and HDBP in the solvent. This problem may be overcome by extracting the H_2MBP and HDBP from the acidified carbonate solutions with 2-ethylhexanol, EHOH, prior to acidification.[480] Laboratory trials indicated that such a process was potentially applicable to Purex waste streams. Problems identified were the formation of precipitates of H_2MBP or HDBP complexes on neutralization of the carbonate solutions and the transfer of some EHOH through the process into the actinide extractant used. The extraction of oxidation state (IV) and (VI) actinides could be accomplished using TBP while DHDECMP could be used to extract oxidation state (III) actinides and lanthanides also.

No matter which waste management strategy is adopted for the short term control of nuclear fuel cycle wastes, ultimately it is necessary to address the problem of isolating them from the biosphere until the radioactive components have decayed to a low level. In the case of the FPs such as ^{137}Cs and ^{90}Sr, decay will be essentially complete on a timescale of millennia. However, plutonium and americium isotopes, along with ^{99}Tc and ^{237}Np, will only decay on geological timescales exceeding 10^6 years. The storage of materials over such a period will be simplified if the wastes are converted into solid form. Various materials have been considered as waste immobilization media including bitumen, cement, glass and synthetic rock. The European nuclear industries have now developed an immobilization process which involves the evaporation and calcination of HAW followed by its incorporation into blocks of borosilicate glass.[11,14,24] Ringwood and coworkers have carried out laboratory development studies on Synroc, a synthetic titanate matrix derived from hollandite, ($BaAl_2Ti_6O_{16}$), perovskite ($CaTiO_3$) and zirconolite ($CaZrTi_2O_7$), which remains unaltered at 5 kbar and 900 °C.[481] They found that after 55 days the leaching of cesium from this material was over 10^3 times less than from glass and believe that synthetic minerals offer advantages over glasses for very long-term waste immobilization.[482]

Detailed knowledge of the very long-term behaviour of radioisotopes in glasses and synthetic minerals, or of their leaching characteristics, remains sparse. Geochemical studies, and investigations of sites such as Oklo, provide some empirical data but only under uncontrolled conditions. However, such information is a valuable complement to laboratory studies.[483] The chemistry of uranium in borosilicate glass has been investigated[484] and U^{VI} was found to be over four times as soluble as U^{IV} in the melt. Spectroscopic studies indicated that the U^{VI} present was associated with the UO_2^{2+} moiety while U^V was in a tetragonally distorted six-coordinate environment and U^{IV} in an eight-coordinate environment. In the presence of Ti^{III}, U^{VI} and U^V were unstable, being reduced to U^{IV}.[485] The leach rate of borosilicate glasses was found to be highly temperature dependent, increasing from 10^{-7}–10^{-6} g cm^{-2} d^{-1} at 5 °C to 10^{-4}–10^{-3} g cm^2 d^{-1} at 100 °C.[24]

Studies of the speciation of actinides in environmental waters are made difficult by the very low concentrations involved and the possibility that minor, undetected contaminants may dominate the binding of a particular metal ion. The environmental behaviour of the actinides has been reviewed.[486] Americium and thorium exhibit simpler behaviour than other actinides since their oxidation states under such conditions are limited to Am^{III} and Th^{IV}. Both are readily adsorbed by granitic rocks and tend to exhibit low solubilities.[487] The thermodynamic solubility product of amorphous $Am(OH)_3$ has been measured as $\log K_s = 17.5 \pm 0.3$ and no evidence for amphoteric behaviour or the formation of $Am(OH)_4^-$ was found below pH 13.[488] Stability constants for the binding of Am^{III} to humic acid have been found to vary with the degree of ionization, α, and were given by $\log \beta_1 = 10.58\alpha + 3.84$ and $\log \beta_2 = 5.32\alpha + 10.42$. These were larger than the corresponding values for Eu^{III}.[489] Humic acids also bind Th^{IV} as described in Section 65.2.1.

The environmental chemistries of uranium, protactinium, neptunium and plutonium are complicated by the range of oxidation states which might arise under environmental conditions. In aerated wastes, uranium will be present mainly as U^{VI} solubilized by complexing anions such as CO_3^{2-} as described in Sections 65.2.1 and 65.2.2.1(i). The dissolution of uranium from irradiated UO_2 fuel over 500 d has been studied[34] and the fractional release rate in air was found to increase from *ca.* 10^{-9} d^{-1} in distilled water to *ca.* 10^{-7} d^{-1} in granitic groundwater. The release rates for plutonium did not change in this way, being between 10^{-7} and 10^{-8} d^{-1} in both cases. Release rates for ^{137}Cs and ^{90}Sr were *ca.* 10^{-6} d^{-1}. Higher values were found during the first 100 days but after this time release rates had fallen to a more or less steady level. The solubility of hydrous PuO_2 has also been studied[490] and equilibrium constants for dissolution according to equations (211)–(213) were given as $\log K = 56.85 \pm 0.36$, -19.45 ± 0.23 and 35.61 ± 0.39. Thermodynamic calculations[486] indicate that all plutonium oxidation states from (III) to (VI) may contribute to

speciation in natural waters. In marine waters, $PuO_2(OH)_2(HCO_3)^-$ and $PuO_2(OH)_2$ were found to be the principal species with some $PuO_2(CO_3)_2^{2-}$ also being present.[491] Other studies have identified PuO_2^+ in natural waters[486] and the solubilization of Pu^{IV} in groundwater has been attributed to fluoride complexing,[492] although subsequent studies[493] indicated that fluoride alone could not account for the observed Pu^{IV} solubility.

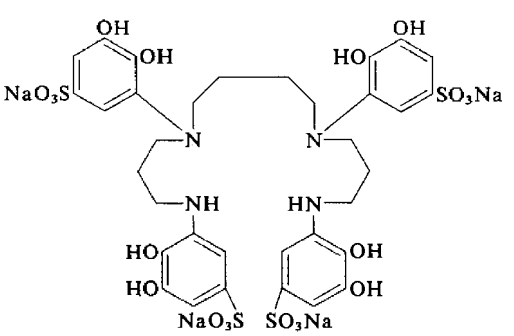
$$PuO_2 \cdot xH_2O \rightarrow Pu^{4+} + 4OH^- + (x-2)H_2O \quad (211)$$

$$PuO_2 \cdot xH_2O \rightarrow PuO_2^+ + e^- + xH_2O \quad (212)$$

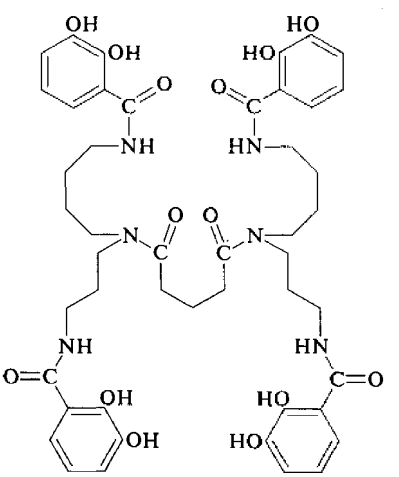
$$PuO_2 \cdot xH_2O \rightarrow PuO_2^{2+} + 2e^- + xH_2O \quad (213)$$

The difficulties of experimentally determining the speciation of actinides present at very low concentrations in natural waters have encouraged the use of computer simulations, based on thermodynamic data, as a means of predicting their speciation and hence their environmental behaviour. The use of modelling techniques to describe the speciation, sorption, solubility and kinetics of inorganic systems in aqueous media has been reviewed in the papers given at an international conference in 1978.[494] Both chemical equilibrium models, exemplified by computer programs such as MINEQL and SOLMNQ, and dynamic reaction path models, exemplified by EQ6, have been developed.[495] Application of the equilibrium models to radioactive waste disposal problems[496] indicates the importance of maintaining low E_h conditions to reduce actinide mobility. At low E_h the actinide oxidation states (III) and (IV) are favoured, leading to low solubilities. However, at higher E_h values, above *ca.* 200 mV for neptunium and *ca.* 500 mV for plutonium, the oxidation state (V) and (VI) species become important and are soluble as carbonate or hydroxycarbonate complexes. The formation of such species greatly increases actinide mobility in groundwater.

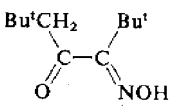
Despite the rigorous containment and control measures used, the industrial handling of the actinides carries with it the possibility of an accidental release or human exposure. In recent years, chemists have been developing actinide specific sequestering agents to expedite the excretion of radiotoxic elements such as plutonium from the body.[497] The specificity of such reagents is of great importance since the binding of biologically essential metals such as Ca^{2+} or Zn^{2+} could give rise to unacceptable side effects. Raymond and coworkers have taken the naturally occurring catecholate and hydroxamate iron sequestering agents as models, from which they have developed a variety of actinide binding agents.[497] Among these the sulfonated tetracatecholamide (**11**) has proved to be especially effective in binding Pu^{IV} without toxic effects.[498] An H-shaped catecholamide (**12**) has also been reported and shows potential as a reagent for environmental americium and plutonium decontamination.[499] Hydroxamate ligands such as (**13**) have also been investigated for binding oxidation state (IV) actinides.[500] An eight-coordinate 4:1 complex was formed with Th^{IV} but reactions with U^{IV} led to an internal oxygen transfer reaction and the formation of a uranyl hydroxamate complex.[500] Uranium sequestering agents have also aroused interest as a means of obtaining uranium from seawater. One example of such a reagent is provided by (**14**), which was found to have selectivities for UO_2^{2+} over Na^+, Mg^{2+}, Ni^{2+} and Zn^{2+} of



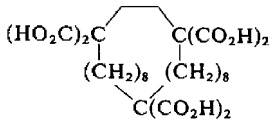
(11)



(12)



(13)



(14)

1.8×10^5, 3.1×10^4, 210 and 80 respectively.[501] However, seawater does not at present offer an economically attractive source of uranium.

The development of reagents to sequester and transport actinides from the bodies of persons accidentally exposed to nuclear materials contrasts with the use of ligands to control the biodistribution of radioisotopes used in medicine. In the former case, water soluble reagents capable of removing the target metal from tissues and allowing its rapid excretion are needed. In the latter case the emphasis is on controlling the biodistribution of a metal which has been complexed before entering the body. Although rapid clearance of the complex from the blood stream may be desirable in this case, accumulation of the complex in a specific organ may be required, as described in the following section.

65.3 PHARMACEUTICAL APPLICATIONS OF RADIONUCLIDES

The first examples of the use of radionuclides in therapy were reported in 1911 and 1913.[502] These involved the injection of radium preparations to treat poorly defined complaints such as skin lesions or arthritis but, in these early cases, it is likely that the radiotoxicity of the doses administered outweighed any therapeutic effects. Subsequently the first radiotracer studies on humans were carried out by Blumgart *et al.*, who monitored arm-to-arm blood circulation times using the radiation emitted from intravenously administered radium C preparations.[502] This work established the medical application of the radiotracer technique, originally demonstrated by Hevesy,[503] and heralded the use of radionuclides in diagnostic medicine. Despite this early activity, nuclear medicine was only able to develop rapidly when specific radionuclides became available from the first cyclotrons and nuclear reactors built in the 1930s and 1940s. Nowadays pure radionuclide preparations play an important role in both therapy and diagnosis and nuclear medicine has become a complex multidisciplinary subject which embraces aspects of physics, chemistry, biology and, in the case of diagnostic imaging applications, computer science. Texts by Horton,[504] Saha[505] and that edited by Tubis and Wolf[16] provide broadly based accounts of the subject. They consider the production of radionuclides, methods of handling and assaying radioactive materials, the formulation and administration of radiopharmaceuticals, the biological effects of ionizing radiations and the equipment used to detect the radiation. They also provide examples of the clinical applications of radiopharmaceuticals.

Radionuclides can be used as external sources of ionizing radiation which may be beamed into particular regions of a patient's body in order to destroy diseased tissue for therapeutic purposes. However, they may also be administered to the patient internally in a variety of ways. Insoluble particles or wires containing a particular nuclide may, for example, be implanted in a region of the body where localized irradiation is required. Alternatively, radionuclides may be adsorbed on, or bound chemically to, the surfaces of particulate materials such as cells, blood platelets or artificially prepared colloids. The resulting radioactive dispersion may then be administered by injection or ingestion. Where the dispersion remains in one site it may be used as a therapeutic aid to irradiate tissue selectively in that region. If, instead, the dispersion is transported around the body by natural processes it is possible to monitor its biodistribution using a suitable detector; the results then provide a diagnostic aid. Another approach is to administer the radionuclide as a component of a dissolved ionic or molecular species which has suitable biodistribution behaviour. In the case of metallic radionuclides, specifically formulated ligands may be used to complex the radioactive metal ions and confer desirable biodistribution behaviour on them. It is this latter approach which exploits the principles of coordination chemistry and which will be considered here.

Coordination compounds have the potential to be used in both diagnostic and therapeutic applications, but only the former have been extensively developed so far. This reflects the differing nature of the two types of application. In diagnosis it is only necessary to detect the location of the radionuclide in the body. Since extremely sensitive devices are available for the detection of ionizing radiation, useful diagnostic information may be obtained with relatively low patient

radiation doses. In contrast, it is the aim of a therapeutic agent to deliver a high radiation dose to the target tissue. Thus, if unacceptably high whole-body radiation doses are to be avoided, highly selective agents must be found which localize rapidly at the target site, and clear very rapidly from the body if unabsorbed. Furthermore, the absorbed material must either remain in place until radioactive decay is virtually complete or, if broken down, must give rise to radioactive products which are rapidly excreted. The performance requirements for therapy agents are thus very exacting and their development poses substantially greater technical problems than that of diagnostic agents.

The suitability of a radionuclide for a particular medical application will depend upon its availability in a radiochemically pure form, its nuclear properties and its chemical properties. In respect of the first of these considerations it is necessary to eliminate any extraneous radiation sources from a material destined for medical use. This need for very high radiochemical purity has a bearing on the means by which the radionuclide is produced. One potential method is by nuclear fission of a heavy element.[506] This approach has the advantage that 'carrier free' radioisotopes of high specific activity may be produced. However, because the process produces a complex mixture of FPs, painstaking separation and purification of the desired radionuclide will be necessary. The problem is simplified somewhat by using a pure target isotope to produce an FP which has rather unique properties. Thus ^{235}U fission produces ^{131}I which may be separated from the other FPs by virtue of its volatility. Fission in pure ^{235}U may also be used to prepare ^{99}Mo in carrier free form, although contamination by ^{103}Ru, ^{131}I and ^{132}Te was a problem in early preparations by this route.[507] Purification by ion exchange chromatography on activated alumina is now used to give a high-purity $^{99}MoO_4^{2-}$ product which is adsorbed on to an alumina column. The ^{99}Mo decays with a 2.78 d half-life to ^{99m}Tc which in turn decays with a 6 h half-life to ^{99}Tc. Elution of the column with saline displaces the TcO_4^- daughters by exchange with chloride but leaves the undecayed $^{99}MoO_4^{2-}$ on the column. This system provides the basis for a ^{99m}Tc generator such as that illustrated in Figure 50. As long as sufficient undecayed $^{99}MoO_4^{2-}$ remains on the

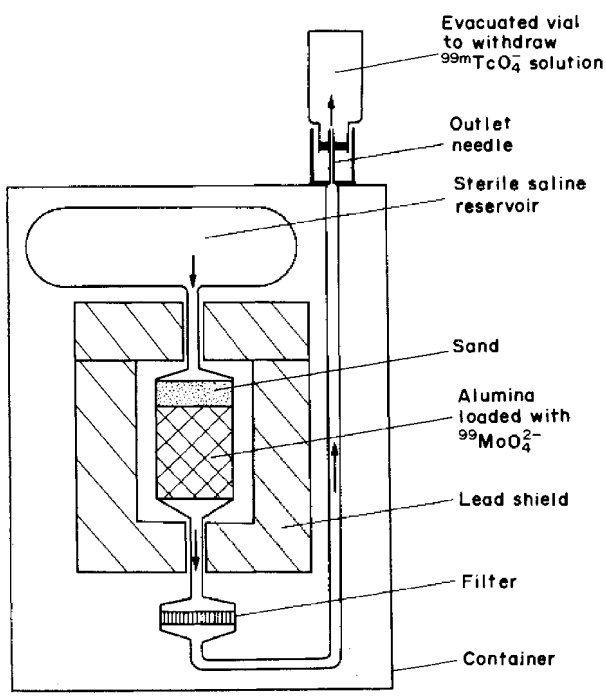


Figure 50 A typical structural arrangement for a $^{99m}TcO_4^-$ generator

column, a sample of $^{99m}TcO_4^-$ may be obtained as required by passing an aliquot of eluant through the column. Such generators are convenient to use and readily transported to clinical laboratories remote from the radionuclide production facility.

An alternative means of radionuclide production employs neutron capture reactions in nonfissile nuclides. Again a high-purity target is used and a mixture of the unconverted target material, the

desired radionuclide and its decay products will result. Irradiation of isotopically enriched ^{98}Mo oxide, for example, produces ^{99}Mo in an (n,γ) reaction. The irradiated material is then dissolved in 40% NaOH solution to give $(NH_4)_2{}^{99}MoO_4$. Treatment with nitric acid and sodium hypochlorite or hydrogen peroxide is used to maintain the oxidation states Mo^{VI} and Tc^{VII} and the mixture is adsorbed on to activated alumina pre-equilibrated with physiological saline. The column is then washed thoroughly and incorporated in a $^{99m}TcO_4^-$ generator.[507] Material produced in this way is not carrier-free so that a portion of the column capacity is taken up by $^{98}MoO_4^{2-}$ and less activity can be incorporated than when fission product $^{99}MoO_4^{2-}$ is used. The problem of FP impurities does not arise with the neutron capture method. However, the presence of impurities in the target may give rise to unwanted products, for example ^{186}Re and ^{188}Re have been detected in the eluate from ^{99m}Tc generators using neutron capture produced ^{99}Mo.[507]

The third means of radionuclide production involves target irradiation by ions accelerated in a cyclotron. One example of this approach is provided by the production of ^{68}Ge, which decays with a 280 day half-life to the positron emitter ^{68}Ga. Proton irradiation of ^{69}Ga produces ^{68}Ge in a (p,2n) reaction. After dissolution of the target material a solution of the ^{68}Ge product in concentrated HCl is prepared and adsorbed on an alumina column which has been pre-equilibrated with 0.005 M EDTA (ethylenediaminetetraacetate) solution. The ^{68}Ga daughter may then be eluted using an EDTA solution in a system which provides the basis of a ^{68}Ga generator. Cyclotron production of radionuclides is expensive compared with reactor irradiations, but higher specific activities are possible than with the neutron capture process. Also, radionuclides with particularly useful properties, and which cannot be obtained from a reactor, may be prepared by cyclotron irradiation. In one example, cyclotron produced ^{52}Fe, a positron emitter, may be used for bone marrow imaging while reactor produced ^{59}Fe, a β-emitter, is unsuitable.[504]

The ionizing radiations emitted by radionuclides may be divided into four types, α, β, β^+ and γ, of which three are of use in diagnostic medicine.[504] The first type, α-particles, are heavy, energetic, dipositive ions which are absorbed in tissue within 10^{-4} m so that a 5 MeV particle would deposit some 5×10^4 MeV m^{-1}, causing the death of any cell through which it passed. Consequently, α-emitters are highly radiotoxic and unsuitable for diagnostic use, although under certain circumstances they may find use in radiotherapy. Radionuclides emitting electrons, β-particles, may also find use in therapy, for example ^{131}I in the treatment of cancer of the thyroid. Since they are lighter and less energetic than α-particles, β-particles have a longer range in tissue, between 10^{-6} and 10^{-3} m, and might typically deposit some 0.25 MeV m^{-1}. The range of the β-particles in tissue is still insufficient for *in vivo* studies using external radiation detectors but they may be used to study organ function where samples, blood or urine for example, can be taken for external analysis. In contrast, β^+ (positron) emitting radionuclides are suitable for studies with external detectors since the positron–electron annihilation process produces two 510 keV γ-rays oriented at 180° to one another. Simultaneous detection of these γ-rays allows an image of the distribution of a β^+ emitter to be obtained by the technique of Positron Emission Tomography, PET. Finally, radionuclides which emit γ-rays from internal nuclear transitions are also of use for diagnostic imaging. A γ-camera consisting of a multihole lead collimator, a scintillating medium and an array of photomultipliers may be used to create an image of the distribution of the γ-emitter within a region of the patient's body.[504] It is in these latter two cases, where external imaging based on γ-ray emission is used as a non-invasive diagnostic technique, that coordination chemistry is finding its greatest level of application in nuclear medicine at present.

The nuclear properties of some metallic radionuclides which have found applications in nuclear medicine are summarized in Table 16. Among these, ^{99m}Tc is by far the most widely used for diagnostic imaging purposes, accounting for some 85% of all nuclear medicine scans in the USA.[20] The pre-eminence of ^{99m}Tc in this role may be attributed to a combination of favourable properties. Firstly, pure $^{99m}TcO_4^-$ is readily available at low cost from generator systems. Secondly, ^{99m}Tc decays with the emission of only a 140 keV γ-ray. This energy is well suited for detection by scintigraphy but is in a range not strongly absorbed by living tissues and so gives low radiation doses to the patient. Thirdly, the decay product, ^{99}Tc, is a long half-life (2.12×10^5 y) low-energy (0.292 MeV) β-emitter of low radiotoxicity. Finally, the chemistry of technetium is varied and allows the formation of a wide range of relatively inert coordination complexes. Among the other radionuclides listed, the isotopes of thallium, gallium and indium are the next most widely used in radiopharmaceutical formulations, while the remaining nuclides find only specialized applications. In addition to those shown in Table 16, a number of other short-lived radionuclides are available from generator systems.[508] These have yet to find a prominent role in radiopharmacy but the nuclear properties of some examples are summarized in Table 17.

Table 16 Some Metallic Radionuclides Used in Nuclear Medicine[503–505,507]

Radio nuclide	*Half life*	*Decay*[a] *mode*	*Principal radiations*	*Energy* (MeV)	*Production*[b] *Method*	*Generator*[c] *parent half life*	*Application*
^{24}Na	2.58 y	β	e^-	1.39	$^{23}Na(n,\gamma)^{24}Na$	—	Exchangeable sodium measurements
			γ	1.37, 2.75			
^{28}Mg	21.1 h	β	e^-	0.5	Cyclotron	—	Magnesium metabolism studies
			γ	1.34, 0.94	$^{26}Mg(\alpha,2p)^{28}Mg$		
				0.40, 0.03			
^{42}K	12.5 h	β	e^-	2.0, 3.6	$^{41}K(n,\gamma)^{42}K$	—	Exchangeable potassium measurements
			γ	1.53			
^{43}K	22 h	β	e^-	0.83	Cyclotron	—	
			γ	0.37, 0.61	$^{40}Ar(\alpha,p)^{43}K$		
^{45}Ca	165 d	β	e^-	0.25	$^{44}Ca(n,\gamma)^{45}Ca$	—	Studies of calcium absorption kinetics
^{47}Ca	4.53 d	β	e^-	2.00, 0.69	$^{46}Ca(n,\gamma)^{47}Ca$	—	
			γ	1.31			
^{51}Cr	27.8 d	EC	γ	0.322	$^{50}Cr(n,\gamma)^{51}Cr$	—	Red blood cell and protein labelling; glomerular filtration rate
^{52}Fe	8.3 h	β^+	e^+	0.81	Cyclotron	—	Bone marrow imaging
		EC	γ	0.51	$^{52}Cr(\alpha,4n)^{52}Fe$		
^{59}Fe	45 d	β	e^-	0.27, 0.46	$^{58}Fe(n,\gamma)^{59}Fe$	—	Iron absorption kinetics
			γ	1.29, 1.10			
^{57}Co	267 d	EC	γ	0.12	Cyclotron	—	Vitamin B_{12} absorption studies
					$^{60}Ni(p,\alpha)^{57}Co$		
^{58}Co	71 d	β^+	e^+	0.49	$^{58}Ni(n,p)^{58}Co$	—	Pernicious anaemia diagnosis
		EC	γ	0.81, 0.51			
^{64}Cu	12.7 h	β	e^-	0.6	$^{63}Cu(n,\gamma)^{64}Cu$	—	Wilson's disease and copper metabolism studies
		β^+	e^+	0.7			
^{67}Cu	61.9 h	β	e^-	0.4, 0.6	Cyclotron	—	Gastrointestinal protein loss
			γ	0.18, 0.09	$^{64}Ni(\alpha,p)^{67}Cu$		

^{65}Zn	245 d	β^+	e^+	0.33	$^{64}Zn(n,\gamma)^{65}Zn$	—	Zinc absorption studies
		EC	γ	1.11, 0.51			
^{67}Ga	78 h	EC	γ	0.30, 0.18	Cyclotron $^{85}Cu(\alpha,2n)^{67}Ga$	—	Imaging of absesses and neoplasms
^{68}Ga	1.13 h	β^+	e^+	1.9	Cyclotron $^{69}Ga(p,2n)^{68}Ge(EC)^{68}Ga$	275 d	Tumor imaging
			γ	1.08, 0.51			
^{75}Se	120 d	EC	γ	0.12, 0.14	$^{74}Se(n,\gamma)^{75}Se$	—	Pancreas imaging
				0.27, 0.28			
				0.40			
^{85}Sr	64 d	EC	γ	0.51, 0.013	Cyclotron $^{85}Rb(p,n)^{85}Sr$	—	Bone scanning
^{87m}Sr	2.83 h	EC	γ	0.39	Cyclotron $^{87}Sr(p,n)^{87}Y(EC)^{87m}Sr$	3.3 d	Bone scanning and bone cancer detection
^{90}Y	64.4 h	β	e^-	2.27	$^{89}Y(n,\gamma)^{90}Y$	—	Treatment of arthritic joints
^{99m}Tc	6 h	IT	γ	0.14	$^{98}Mo(n,\gamma)^{99}Mo(\beta)^{99m}Tc$ or ^{235}U fission $\rightarrow$ ^{99}Mo	2.78 d	Organ imaging; many applications
^{111}In	2.8 d	EC	γ	0.25, 0.17	Cyclotron $^{109}Ag(\alpha,2n)^{111}In$	—	White cell and protein labelling
^{113m}In	1.73 h	IT	γ	0.39	$^{112}Sn(n,\gamma)^{113}Sn(EC)^{113m}In$	115 d	Brain scanning; cardiac output; liver scanning
^{131}Cs	9.7 d	EC	γ	0.034	$^{130}Ba(n,\gamma)^{131}Ba(EC)^{131}Cs$	11.6 d	Myocardial and tumor scanning; peripheral circulation studies
^{197}Hg	64 h	EC	γ	0.19, 0.077	Cyclotron $^{197}Au(p,n)^{197}Hg$	—	Brain scanning
^{203}Hg	46.6 d	β	e^-	0.20	$^{202}Hg(n,\gamma)^{203}Hg$	—	Kidney scanning
			γ	0.28			
^{195m}Pt	4.02 d	IT	γ	0.13, 0.099	$^{194}Pt(n,\gamma)^{195}Pt$	—	Pharmacy research
^{198}Au	65 h	β	e^-	0.96	$^{197}Au(n,\gamma)^{198}Au$	—	Liver scanning; treatment of intraperitoneal neoplasms
			γ	0.41			
^{201}Tl	74 h	EC	γ	0.07	Cyclotron $^{203}Tl(p,3n)^{201}Pb(EC)^{201}Tl$	—	Myocardial imaging

[a] EC = electron capture, IT = internal transition.
[b] Neutron irradiation in a reactor unless otherwise specified.
[c] Some radionuclides are available from generators, which makes them conveniently available for widespread clinical use. The life of the generator varies with the half life of the parent of the generator-produced radionuclide.

Table 17 Some Short-lived Radionuclides Available from Generators[508]

Radio nuclide	*Half life*	*Decay*[a] *mode*	*Principal radiations*	*Energy* (MeV)	*Production*[a] *method*	*Generator parent half life*
^{28}Al	2.3 m	β	e^-	2.9	Cyclotron	21.2 h
			γ	1.78	$^{26}Mg(\alpha,2p)^{28}Mg(\beta)^{28}Al$	
^{44}Sc	3.92 h	β^+	e^+	1.5	Cyclotron	47.3 y
		EC	γ	1.16, 0.51	$^{45}Sc(p,2n)^{44}Ti(\beta^+)^{44}Sc$	
^{47}Sc	3.43 d	β	e^-	0.4, 0.6	Reactor	4.5 d
			γ	0.16	$^{46}Ca(n,\gamma)^{47}Ca(\beta)^{47}Sc$	
^{82}Rb	1.3 m	β^+	e^+	3.2, 0.8	Cyclotron	25 d
		EC	γ	0.78, 0.55, 0.62	$^{85}Rb(p,4n)^{82}Sr(EC)^{82}Rb$	
^{109m}Ag	39.6 s	IT	γ	0.088	Cyclotron	1.24 y
					$^{109}Ag(d,2n)^{109}Cd(EC)^{109m}Ag$	
^{128}Cs	3.8 m	β^+	e^+	2.9	Cyclotron	2.43 d
		EC	γ	0.53, 0.44	$^{133}Cs(p,6n)^{128}Ba(EC)^{128}Cs$	
^{137m}Ba	2.55 m	IT	γ	0.66	^{235}U fission $\rightarrow$ $^{137}Cs(\beta)^{137m}Ba$	30 y
^{191m}Ir	4.9 s	IT	γ	0.13	Reactor	15 d
					$^{190}Os(n,\gamma)^{191}Os(\beta)^{191m}Ir$	
^{195m}Au	30.6 s	IT	γ	0.26	$^{197}Au(p,3n)^{195m}Hg(EC)^{195m}Au$	1.67 d

[a] EC = electron capture, IT = internal transition.

65.3.1 Chemical Aspects of Radiopharmaceutical Agents

Not all radiopharmaceutical applications of metallic radionuclides require the prior complexation of the metal ion with a ligand designed to control its biodistribution. In the case of some metal ions, present naturally in the body, it may be desirable to administer solutions of simple salts in order to monitor their absorption and distribution using the radiotracer technique. This approach may be used to monitor sodium or potassium absorption, for example.[509] It has also been used to study Wilson's disease by the administration of ^{64}Cu acetate,[570] ferrokinetics using a ^{59}Fe citrate formulation[511] and zinc uptake from food[512] using bread prepared with $^{65}ZnCl_2$. In these cases the natural coordination chemistry processes occurring *in vivo* are exploited to study the metabolism of the trace metal. Similarly, metal ions not normally present in significant amounts *in vivo* may be administered as simple salts and their tendency to accumulate in organs as a result of *in vivo* processes may be exploited. Thus ^{87m}Sr nitrate has been used for bone imaging[513] and ^{201}Tl chloride for myocardial imaging.[514] The natural biodistribution behaviour of these artificially introduced elements is thereby utilized without recourse to the addition of specifically formulated chelating agents. However, in some cases it may be necessary to add chelating ligands to retain the radioactive metal ion in a form suitable for administration to the patient, and to suppress hydrolysis reactions. The use of citrate in the ^{59}Fe formulation mentioned above, and in the preparations of gallium isotopes used in nuclear medicine,[515] provides an example of this. The citrate complex is broken down *in vivo*, releasing the metal ion, but it provides a convenient vehicle for introducing the metal ion into the patient's body.

Ligands which are used to bind a radioactive metal ion in a complex which does not rapidly dissociate *in vivo*, and thus to control the metal distribution, may be divided into three broad types. Firstly, there are naturally occurring chelating agents which may be extracted and used to prepare radiopharmaceuticals which exhibit specific *in vivo* properties. Perhaps the best example of this is provided by the preparation of ^{57}Co or ^{58}Co labelled cyanocobalamin for the investigation of cobalt uptake and pernicious anaemia.[516,517] Ceruloplasmin labelled with ^{67}Cu has similarly been utilized in studies of gastrointestinal protein loss.[518] Other examples of this first type of ligand are provided by the bleomycins, naturally occurring glycopeptides which exhibit antitumor activity.[519] Since the bleomycins were known to accumulate selectively in certain cancer cells, and to bind metal ions, they offered promise as agents to carry radionuclides into tumors. Most bleomycin metal complexes have proved rather labile *in vivo* but a kinetically inert complex could be prepared with Co^{3+}, allowing the production of a ^{57}Co labelled bleomycin.[19] Unfortunately the properties of ^{57}Co are not ideal for clinical applications and an alternative approach to utilizing the tumor localizing properties of bleomycin was investigated.[19] This involved the attachment of a derivative of EDTA to the protein region of bleomycin A_2. The resulting molecule, BLEDTA, exemplifies the second type of ligand available to radiopharmacy. That is a naturally occurring

material which has been chemically modified to incorporate a chelating group capable of binding a metal ion. In the bleomycin example, BLEDTA was used to bind ^{111}In to produce a radiopharmaceutical with potential applications as a tumor imaging agent. Agents of this type have not been extensively developed as yet. However, the increasing availability of monoclonal antibody preparations offers an important source of natural proteins with specific *in vivo* distribution properties. The modification of such substrates, by condensation with the cyclic anhydride of diethylenetetraaminepentaacetic acid (DTPA anhydride) for example,[520] should provide a range of new ligands for radiopharmaceutical use. This topic is considered in more detail in Section 65.3.2.6.

The majority of ligands used in radiopharmaceutical formulations at present are of the third type, *i.e.* artificial complexing agents of synthetic origin. The *in vivo* behaviour of the complexes formed by such agents cannot readily be predicted and must be determined by experiment. Furthermore, the biodistribution of the metal complex and of the free ligand may typically be quite different. To be an effective diagnostic agent a ligand must form a complex with the radioactive metal ion which remains intact *in vivo*. This complex must then selectively accumulate in the target tissue, carrying a substantial proportion of the radioactivity administered to this site. Finally, any of the complex not accumulated should clear rapidly and completely from the blood stream to minimize background radiation. The discovery of agents which meet these criteria has, in large part, been due to serendipity, although recent studies of structure–biodistribution relationships are allowing some broadly based predictions to be made. Complexes involving synthetic ligands may also be used to study the *in vivo* behaviour of drugs which normally contain nonradioactive metals. Examples of this are provided by the preparation of ^{195m}Pt labelled *cis*-dichlorodiamineplatinum(II) anticancer drugs[521,522] and ^{195}Au labelled gold anti-arthritis drugs.[523]

In order that a complex of a radioactive metal should remain intact *in vivo*, either the metal ion must exhibit kinetically inert behaviour, or the complex must have a very high stability constant. Otherwise the many potential metal ion binding sites present *in vivo* may thermodynamically compete for the metal. The radionuclides used in nuclear medicine are of high specific activity, 1.94×10^{11} Bq μg^{-1} in the case of ^{99m}Tc. Accordingly they will be present *in vivo* at very low concentrations; 10^{-10} M or less might be typical for a carrier free preparation. Under these conditions the binding sites on serum proteins will be present in great stoichiometric excess over the artificial ligand, so that the metal ion could be lost from a labile complex through mass action effects alone. Also, metals such as Fe^{III} are present *in vivo* so there also exists a possibility that such ions might compete with the radioactive metal ion for the ligand. The principal metals used in diagnostic formulations are isotopes of technetium, gallium and indium. The latter two metals exist as oxidation state (III) ions under physiologically relevant conditions and behave as hard Lewis acids. Consequently they are kinetically labile in their chemistry and only form complexes of high stability with polydentate chelating agents such as EDTA or DTPA. In contrast, technetium can form kinetically inert complexes so that even certain unidentate ligand complexes may be suitable for radiopharmaceutical use with this metal. Technetium may also exist in a variety of oxidation states, thus allowing a wide range of stable or inert complexes to be prepared. This versatility, combined with its favourable nuclear properties, results in technetium having the potential for use in a wide variety of diagnostic imaging applications.

65.3.1.1 Gallium and indium

The coordination chemistry of gallium and indium has been reviewed in Chapters 25.1 and 25.2. Other reviews relating specifically to radiopharmaceutical applications have been provided by Thakur,[524] more recently by Moerlein and Welch[23,515] and, in the case of indium, by Kaempfer.[525] Reviews of the development of radiopharmaceuticals based on short-lived radionuclides other than ^{99m}Tc have also been provided by Hnatowich[526] and by Silvester.[18] Only oxidation state (III) is important for gallium and indium under physiological conditions. The ionic radii of Ga^{3+} and In^{3+} are reported[527] to be 0.62 and 0.80 Å respectively, compared with a value of 0.65 Å for high-spin Fe^{3+}. Since high-spin Fe^{3+} is a d^5 system, having no ligand field stabilization energy, its aqueous chemistry is rather like that of Ga^{3+}, which is a d^{10} system of similar size. The larger In^{3+} ion also shows some similarities to Fe^{3+} in its behaviour. All three ions may be described as hard 'class a' acceptors which form more stable complexes with oxygen donor ligands. Their complexes are labile and the ions are prone to hydrolysis in aqueous media, forming highly insoluble precipitates of the trihydroxide. Precipitation of $^{67}Ga^{3+}$, $^{68}Ga^{3+}$, $^{111}In^{3+}$ and $^{52}Fe^{3+}$ is

Table 18 Selected Formation Constants[528]

Ligand	*log K_1*	
	In^{3+}	*Ga^{3+}*
Cl^-	2.44	0.01
OH^-	11.9	11.1
Acetate	3.50	—
Oxalate	5.30	6.45
Citrate	6.18	10.02
NTA[a]	15.9	13.6
HEDTA[b]	17.2	16.9
EDTA	25.3	20.3
DTPA	28.4	25.54
Oxine[c]	—	14.5

[a] Nitrilotriacetate.
[b] 2-Hydroxydiaminoethanetriacetate.
[c] 8-Hydroxyquinoline.

expected to occur above pH = 4.48, 5.10, 5.22 and 3.86 respectively in aqueous solutions containing 3.7×10^8 Bq dm^{-3} of carrier free radionuclide.[23] This means that in solutions at physiological pH a complexing agent must be added to suppress precipitation and retain the metal ions in solution. Since gallium exhibits amphoteric behaviour, $Ga(OH)_3$ will redissolve in solutions above pH 10 but this is outside the normal physiological pH range.

Polydentate ligands containing carboxylate groups form complexes with Ga^{3+} and In^{3+} which exhibit both thermodynamic and kinetic stability. Some equilibrium constants for the formation of such complexes are given in Table 18 and show an increase in thermodynamic stability with increasing numbers of carboxylate groups in the polyfunctional amine acetate series.[528,529] Among these complexes only the In^{3+}-DTPA complex is actually stable with respect to the free ligand and the metal hydroxide in aqueous media, as shown in Table 19. However, the kinetics of the hydrolysis reactions are slow so that Ga^{3+} complexes with EDTA and DTPA are sufficiently inert to be of clinical use. The kinetics of formation of the EDTA and DTPA complexes are also slow and the precipitation of $Ga(OH)_3$ or $In(OH)_3$ will pre-empt the complexation reaction at pH values high enough to permit complexation. To avoid this a complex of intermediate stability is first formed, for example with citrate, to suppress precipitation at the higher pH. This complex may then undergo a thermodynamically driven exchange reaction with the intended final ligand. In this way, complexes of Ga^{3+} or In^{3+} radionuclides may be prepared which have sufficient stability at physiological pH and which are suitable for administration to a patient. Stability constant data for complex formation with Ga^{3+} and In^{3+} are somewhat limited compared with those for Fe^{3+}. Welch has exploited the similarities in the chemistries of these ions in developing[23,528] the empirical equations (214) and (215) to relate the equilibrium constants K_{Ga}

$$\log K_{In} = -0.5854 + 1.0108 \log K_{Fe} \tag{214}$$

$$\log K_{Ga} = 0.9624 + 0.8397 \log K_{Fe} \tag{215}$$

Table 19 Equilibrium Constants for Ligand Exchange in Gallium and Indium Complexes[23]

Reaction[a]	*L*	*log K*		
		$M = Fe^{3+}$	*Ga^{3+}*	*In^{3+}*
$ML + 3OH^- \rightleftharpoons M(OH)_3 + L^{3-}$	EDTA	9.1	10.6	4.3
	DTPA	6.2	5.4	0.3
$ML + Tf^{3-} \rightleftharpoons M{-}Tf + L^{3-}$	EDTA[b,c]	4.9	3.4	5.5
	DTPA[c,d]	2.3	−1.8	1.5
$M{-}Tf + 3OH^- \rightleftharpoons M(OH)_3 + Tf^{3-}$	Tf	3.9	7.2	−1.2

[a] Tf = Transferrin.
[b] At equilibrium, log {[M—Tf]/[ML]} = 6.0 for Fe^{3+}, 4.5 for Ga^{3+} and 6.6 for In^{3+}.
[c] Calculated assuming the injection of 4×10^{-6} mole of free ligand and an unbound transferrin pool of 5×10^{-5} mole.
[d] At equilibrium, log {[M—Tf]/[ML]} = 3.4 for Fe^{3+}, −0.7 for Ga^{3+} and 2.6 for In^{3+}.

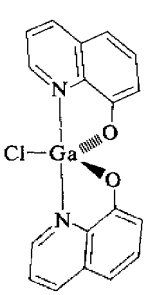
and K_{In}, for complex formation with Ga^{3+} and In^{3+} respectively, to K_{Fe}, the formation constant for the analogous Fe^{3+} complex. On this basis, stability constants for Ga^{3+} and In^{3+} may be estimated in the absence of experimental data by using results reported for Fe^{3+} systems.

The similarities between Ga^{3+}, In^{3+} and Fe^{3+} are manifest *in vivo* by the binding of all three ions to the serum protein transferrin, Tf, normally used for iron transport. The formation constant for the Ga^{3+}-Tf complex has been found[530] to be $10^{23.7}$ and Welch has calculated[23] values for the equilibrium constants for the exchange of trivalent metal ions between EDTA or DTPA and Tf as shown in Table 19. These figures show that only the DTPA complex of Ga^{3+} is stable with respect to metal exchange with Tf. Table 19 also shows values for the equilibrium exchange reaction between Tf and hydroxide ion.[23] These indicate that, while the indium–Tf complex should be stable to hydrolysis *in vivo*, in the long term the insoluble $Ga(OH)_3$ should form from the Ga^{3+}-Tf complex, this instability having been confirmed experimentally.[531,532]

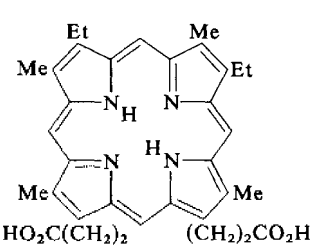
Early attempts to utilize gallium radioisotopes in diagnostic medicine involved lactate complexation, but this was superseded by the use of citrate formulations which were easier to prepare.[524] Experiments involving gallium preparations which were not carrier free gave rise to the accumulation of radioactivity in bone. However, subsequent studies with carrier free ^{67}Ga citrate showed much lower bone uptake and it was found[533] that bone deposition was enhanced when the plasma Tf was saturated with Ga^{3+}. At the lower concentrations involved in carrier free preparations, all the gallium was bound by transferrin and rendered unavailable for bond deposition, whereas when larger quantities of gallium were administered the binding capacity of the transferrin became saturated and the excess gallium could then be deposited in bone. In 1969 it was found that ^{67}Ga citrate injection led to ^{67}Ga accumulation in soft tissue tumors[534] and this has since proven to be a major application of gallium radiopharmaceuticals. In the case of indium, ^{111}In injected as the chloride salt was also found to accumulate in bone and in soft tissue tumors.[524] Again binding to transferrin appeared to be an important transport mechanism for this element and ^{111}In citrate formulations have been used for bone marrow imaging.[535]

In recent years a variety of ligands have been investigated as potential agents for expanding the range of applications for gallium and indium radioisotopes. The bidentate chelating ligand 8-hydroxyquinoline (oxine) is prominent among these since it can form neutral tris complexes with Ga^{3+} and In^{3+}. Being neutral these complexes are lipophilic and may penetrate cell membranes so that $^{111}In(oxine)_3$ may be used to label leukocytes, for imaging absesses,[524] or to label blood platelets.[23,536] Similarly, $^{68}Ga(oxine)_3$ has been used to label red blood cells.[537] Structural data on oxine and related ligand complexes of Ga^{3+} or In^{3+} is limited. Single-crystal diffraction studies of the five-coordinate complexes chlorobis(2-isopropyl-8-mercaptoquinolinato)indium(III)[538] and chlorobis(2-methyl-8-hydroxyquinolinate)gallium(III)[539,540] have been carried out. The gallium complex was found to adopt the distorted trigonal bipyramidal structure (**15**) with the chloride ligand and two oxygen atoms occupying the equatorial plane. The indium complex adopted a similar structure. Another ligand used to produce a water-soluble ^{111}In scanning agent is *meso*-protoporphyrin IX (**16**); this agent also allows the ^{111}In labelling of hemoglobin to be effected.[541] Several structural studies of In^{3+} complexes with 5,10,15,20-tetraphenylporphyrinate have been reported.[542–544] In the complex containing the chloroindium(III) moiety[543] the indium is in a square pyramidal coordination environment in which the indium lies 0.61 Å above the mean plane defined by the four porphyrin nitrogen atoms. The complex containing the methylsulfonate ion is polymeric, with the anion bridging between the indium centres.[544] In this case the indium is located exactly in the plane of the nitrogen atoms, although ^1H NMR studies indicated that this structure is not maintained in dilute solutions.

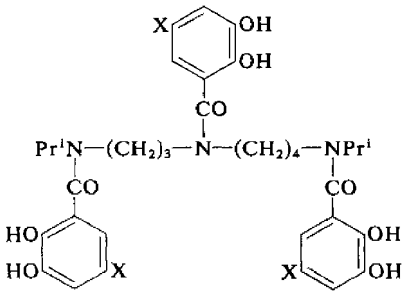
Recently the naturally occurring powerful iron sequestering agent enterobactin has provided a model for the development of ligands which show high formation constants with Ga^{3+} and



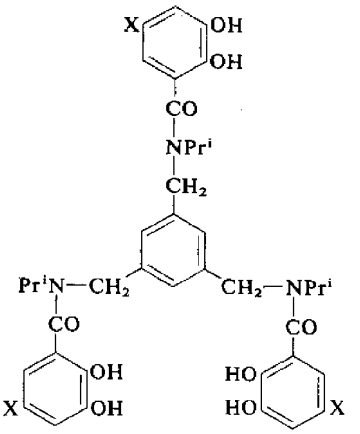
(15)



(16)



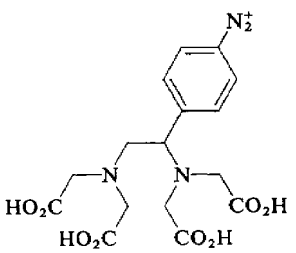
(17) X = H; 3,4-DiP-LICAM
X = SO_3^-; 3,4-DiP-LICAMS



(18) X = H; TiP—MECAM
X = SO_3^-; TiP—MECAMS

In^{3+}. These tricatecholate ligands, having the structures (**17**) and (**18**), exhibit formation constants of 10^{38} or more with Ga^{3+} and In^{3+}. The 3,4-DiP-LICAMS and TiP-MECAMS complexes were found to clear from the body primarily through the kidneys, while the less polar 3,4-DiP-LICAM and TiP-MECAM complexes cleared *via* the liver.[545] Experiments indicate that such ligands may find application in clearing radioisotopes of gallium or indium from the blood after their administration for imaging purposes. This reduces background radiation and improves the quality of the target organ image. The mechanism of metal ion release from ligands of this type at low pH has been found[546] to involve a series of stepwise protonation reactions. Protonation of a phenolic oxygen in the position *meta* to a salicylamide group resulted in a shift of the metal to a coordination site between the remaining phenolic oxygen and the oxygens of the salicylamide carbonyl groups. Further protonations would then lead to the complete release of the metal ion from the catecholate groups and dissociation of the complex.

Another development in the application of coordination chemistry to gallium and indium radiopharmacy has been the synthesis of the bifunctional ligand (**19**). This may be linked to a protein *via* the diazo group to give a product which can bind $^{111}In^{3+}$ using the EDTA moiety. In this way, labelled human serum albumin was prepared and found to be largely stable with respect to $^{111}In^{3+}$ exchange with transferrin over a period of two weeks.[547] This reagent thus offers an alternative to DTPA anhydride for protein or antibody labelling, although its utility in this context remains to be fully established. A structural study[548] of the complex $Na_3[In(EDTA)(SO_3)]\cdot 4H_2O$ has revealed a coordination number of 7 for the In^{3+} ion. The coordination geometry consisted of an approximately trigonal prismatic arrangement of the two nitrogen and four carboxylate oxygens of the EDTA, with one face capped by an oxygen from a pyramidal SO_3^{2-} ion. It would seem, therefore, that EDTA alone is unable to fully saturate the In^{3+} coordination sphere, so that this ligand may not be an ideal choice for incorporation in bifunctional reagents for the ^{111}In or ^{113m}In labelling of proteins. However, the development of reagents such as (**19**) and DTPA anhydride, combined with the availability of ^{68}Ga and ^{113m}In from generator systems, would suggest that there is scope for expanding the clinical application and usage of these radionuclides.



(19)

65.3.1.2 Technetium

Unlike gallium and indium, technetium may exist in a variety of oxidation states under physiological conditions, depending upon the nature of the ligands by which it is complexed.

Complexes of technetium in oxidation states ranging from (−I) to (VII) have been prepared chemically and characterized. However, historically only the higher oxidation states (IV), (V) and (VII) have been of major importance in radiopharmaceutical formulations. More recently there has been increased interest in lower oxidation state technetium complexes for medical applications, and the use of π-acceptor ligands has allowed the preparation of Tc^{I} complexes which are stable *in vivo*. The coordination chemistry of technetium has been described in Chapter 42 and recent reviews have been provided by Davison[21] and by Schwochau.[22] Reviews which relate to medical applications of technetium are given by Jones and Davison,[549] Deutsch *et al.*,[20] Deutsch and Barnett,[550] Siedel[551] and Clarke and Fackler.[552] The *in vivo* chemistry of ^{99m}Tc chelates has been described by Eckelman and Volkert,[553] while the structures of technetium complexes, determined by X-ray diffraction techniques, have been reviewed by Bandoli *et al.*[554]

Technetium is unique among the *d*-block elements in that it has no stable isotope. Thus chemical studies of its longest lived isotope, ^{99}Tc, must be carried out in a radiochemical laboratory. The long half-life (2.12×10^5 y) and weak β-emission (0.292 MeV) of ^{99}Tc mean that it can be handled at the mCi (3.7×10^7 Bq) level without special precautions, other than those normally required for contamination control and compliance with legislation relating to radioactive materials.[22,555] The walls of laboratory glassware, heavy duty rubber gloves, laboratory coat and safety spectacles provide adequate radiation shielding at this level of activity. The major potential hazards relate to the spread of contamination, especially from dusty or volatile compounds, and the consequent risk of ingestion. The use of monitored fume cupboard and radiochemistry laboratory facilities is thus necessary. The specific activity of ^{99}Tc is 6.29×10^7 Bq g^{-1} and scintillation counting offers a convenient means of analyzing solutions for this isotope.[556] The medically used isotope, ^{99m}Tc, is normally obtained as a solution of $^{99m}TcO_4^-$ in physiological saline (NaCl) from a generator system. Depending on the age and frequency of use of the generator, the eluate will also contain a proportion of ground state $^{99}TcO_4^-$, so that the overall TcO_4^- concentration may fall in the range 10^{-8}–10^{-6} M.[20] The handling of ^{99m}Tc containing solutions in nuclear medical applications has been described in several texts.[16,504,505,551]

The $^{99m}TcO_4^-$ obtained from the generator has itself been used for diagnostic purposes, but its applications are limited. Intravenously infected TcO_4^- is often assumed to have a whole body biological half life of about 2 days. However, it leaves the blood with a half life of minutes, probably by equilibration with intercellular fluids. A slower process also leads to the intracellular permeation of the TcO_4^-. A three-compartment model based on migration between blood and tissue and elimination from blood into urine has been proposed[557] to describe the transfer of TcO_4^- in man. The principal sites of accumulation are the thyroid and salivary glands as well as the stomach.[551] The thyroid uptake mechanism may be similar to that for I^- but the TcO_4^- does not become chemically bound and so may be subsequently eliminated. The TcO_4^- ion has a tetrahedral structure[558,559] and is displaced from the thyroid by the structurally similar anion ClO_4^-.[551] In addition to thyroid scanning, $^{99m}TcO_4^-$ has been used for brain scanning since, although TcO_4^- does not penetrate the blood brain barrier, it does accumulate to some extent in regions where this barrier is disturbed, for example by a tumor.[551]

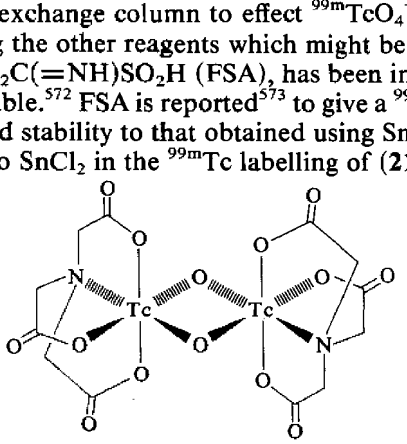
In most medical applications the $^{99m}TcO_4^-$ will be reduced to a lower oxidation state and bound to a carrier prior to administration. The carrier may be a particulate material, a chemically modified biological material or a ligand which produces a classical coordination complex. This latter type of radiopharmaceutical is sometimes referred to as 'technetium essential' since its biodistribution is uniquely defined by the nature of the technetium complex itself. Electrochemical studies of the TcO_4^- reduction mechanism have been largely inconclusive, many failing to take account of the chemical reaction between TcO_4^- and mercury used as an electrode material.[560] In the absence of complexing agents, reduction of TcO_4^- in aqueous media occurs at *ca.* +0.6 V (*vs.* NHE) and is a multielectron irreversible process leading to TcO_2 or Tc_2O_3 formation.[561] Direct electron transfer occurs on mercury electrodes but on platinum, or gold, hydrogen is produced which then effects the reduction. In non-aqueous solvents, different behaviour is observed and in acetonitrile, controlled potential electrolysis affords the violet air-sensitive Tc^{VI} complex $[Me_4N]_2[TcO_4]$.[562] Potential *versus* pH diagrams indicating the thermodynamically preferred reduction products for different aqueous TcO_4^- concentrations have been calculated to summarize the results of the polarographic studies.[563] If the electrochemical reduction of TcO_4^- is carried out in the presence of complexing ligands, lower oxidation state complexes may be prepared in aqueous media. In one such example a complex with EDTA was prepared[563] by reduction at a mercury electrode at pH 10, conditions normally unsuitable for chemical reduction reactions.

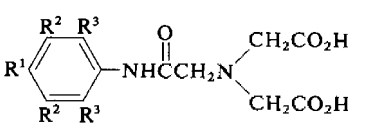
Although electrochemical reductions can be used in the preparation of ^{99m}Tc radiopharmaceuticals, for reasons of convenience chemical reduction is usually the method of choice. A

wide variety of reducing agents has been used in the chemical preparation of lower oxidation state ^{99}Tc complexes. These include metal ions such as Fe^{2+} or Sn^{2+}, inorganic compounds such as $S_2O_4^{2-}$, BH_4^- or N_2H_4 and organic substances such as tertiary phosphines or formamidinesulfinic acid.[20] A study of Tc^{VII} and Tc^{IV} reduction in strongly acidic aqueous media containing non complexing anions found that reduction to Tc^{II} was possible under such conditions.[564] However, the lower oxidation state species produced were unstable and not necessarily monomeric. At higher pH it was necessary to carry out the reduction in the presence of a complexing ligand if the precipitation of TcO_2 was to be avoided. The selection of a reducing agent for use in a radiopharmaceutical formulation will be restricted by considerations of the reduction kinetics, the complexity of the ^{99m}Tc product distribution and by the toxicity of the reductant or its reaction products. At present, Sn^{II}, in the form of $SnCl_2$, is the most widely used reductant in medical applications of ^{99m}Tc.

The chemistry of the $^{99m}TcO_4^-$ reduction and complexation process in a radiopharmaceutical preparation will usually be complicated. More than one technetium oxidation state may be produced and a variety of ^{99m}Tc complexes may form, even with a single complexing agent. Furthermore dinuclear or oligomeric complexes may form and it is possible for the reductant or its reaction products to become incorporated in the ^{99m}Tc complex and thus alter its *in vivo* behaviour. The following examples serve to illustrate these points. A study of the products formed by Sn^{II} reduction of generator produced $^{99m}TcO_4^-$, in the presence of various ligands, indicated[565] that Tc^V species were formed with gluconate, citrate or mannitol as the complexing ligands but that with pyrophosphate and hydroxy ethane-1,1-diphosphonate (HEDP), Tc^{IV} species were favoured. At Sn^{II} concentrations of 2 $\mu g\ dm^{-3}$ or less, Tc^V appeared to be the dominant oxidation state produced, but at higher concentrations Tc^{IV} and even Tc^{III} could be formed. Other workers have also reported[566] the formation of both Tc^V and Tc^{IV} species in the presence of acids such as citric, malic, tartaric and gluconic. In reactions involving DTPA they were able to identify a cationic Tc-DTPA complex at pH <1.8 or an oligomeric Tc-DTPA complex at higher pH. The latter exhibited an IR band at 810 cm^{-1}, assigned to a Tc—O—Tc moiety. In the presence of EDTA an anionic complex was produced which appeared to be monomeric, while with NTA a dimeric product was obtained for which a structure containing a $Tc_2(\mu\text{-}OH)_2$ core was proposed. A similar product was formed by SO_2 reduction of $^{99}TcO_4^-$ in the presence of NTA.[567] An X-ray diffraction study of this material revealed the structure (**20**), which contained two $\mu\text{-}O^{2-}$ ligands and a Tc—Tc distance of 2.363 Å. A well established example of the incorporation of the $SnCl_2$ reductant into a technetium complex is provided by the reaction with dimethylglyoxime ($DMGH_2$). This afforded $[Tc(DMG)_3(SnCl_3)(OH)]$, having the structure illustrated in Figure 51.[568] The state of protonation of the DMG^{2-} ligand was uncertain but the structure clearly demonstrated the ability of the tin to bind to oxygens in the ligands attached to technetium and to what was presumably a Tc=O oxygen before complexation of the tin. Whether or not it becomes incorporated in technetium complexes, a proportion of the tin present in a radiopharmaceutical formulation will be injected into the patient. This may result in toxic or other undesirable side effects, as described in a review of the *in vivo* behaviour of tin.[569] A more controlled reduction method which, unlike $SnCl_2$ preparations, does not require anaerobic conditions has been proposed based on the electrolytic generation of Sn^{2+} from a tin wire.[570] This requires lower tin concentrations to affect $^{99m}TcO_4^-$ reduction and thus minimizes the quantity of tin injected. An alternative means of avoiding tin incorporation in the administered radiopharmaceutical is to use Sn^{II} adsorbed on a cation exchange column to effect $^{99m}TcO_4^-$ reduction.[571]

Among the other reagents which might be applied to $^{99m}TcO_4^-$ reduction, formamidinesulfinic acid, $NH_2C(=NH)SO_2H$ (FSA), has been investigated for use in alkaline media, in which $SnCl_2$ is unsuitable.[572] FSA is reported[573] to give a ^{99m}Tc labelled glucoheptonate preparation of superior purity and stability to that obtained using $SnCl_2$. However, other workers[574] found that FSA was inferior to $SnCl_2$ in the ^{99m}Tc labelling of (**21a**) and proposed that FSA, or its reaction products,





(**21a**) $R^1 = R^2 = R^3 = H$; HIDA
(**21b**) $R^1 = R^2 = H$, $R^3 = Me$
(**21c**) $R^1 = R^2 = H$, $R^3 = Et$

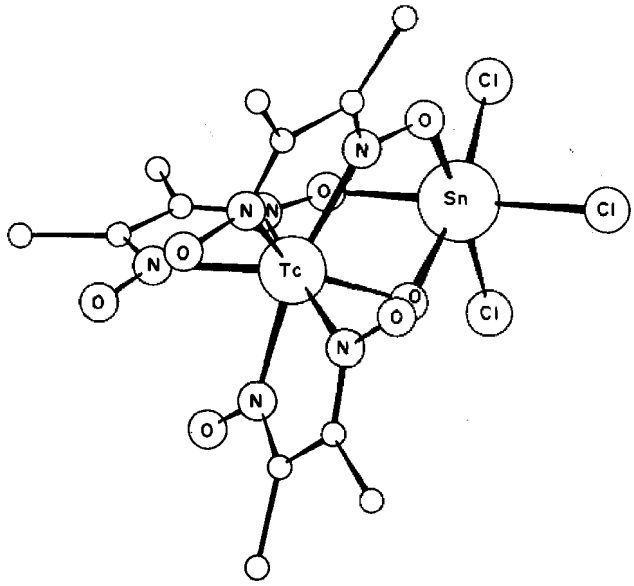
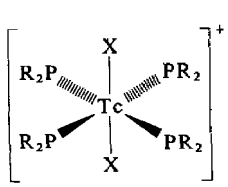


Figure 51 The structure of $[Tc(DMG)_3SnCl_3(OH)]$.[554] (Reproduced from G. Bandoli, U. Mazzi, E. Roncari and E. Deutsch, *Coord. Chem. Rev.*, 1982, **44**, 191, with permission from Elsevier Science Publishers)

could complex the reduced technetium. Subsequently, a study of the rate of formation of the glucoheptonate complex indicated[572] that a base catalyzed degradation of FSA was initiated at pH 9.5, giving rise to intermediates which were oxidized to urea and sulfite. This resulted in an induction period of *ca.* 10 minutes for the formation of the glucoheptanate complex from TcO_4^-, with the reaction being largely complete after 20 minutes. In contrast, the reaction was almost instantaneous in the presence of $SnCl_2$.

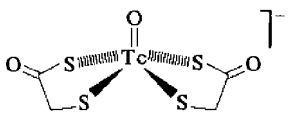
It is often found that different reducing agents will give different biodistribution behaviour for ^{99m}Tc preparations based on the same complexing agent. Even changes in the conditions of preparation may give rise to varying results using the same reducing agent. Chemical examples of such behaviour are provided by the reaction of TcO_4^- with diethyldithiocarbamate (Et_2dtc^-) in the presence of different reducing agents. When dithionite, $S_2O_4^{2-}$, was used a dinuclear Tc^V complex, $[\{TcO(Et_2dtc)_2\}_2(\mu\text{-}O)]$, formed while hydrazine afforded the Tc^V nitride, $[TcN(Et_2dtc)_2]$, and FSA gave a Tc^{III} complex, $[Tc(Et_2dtc)_3]$.[552,574,575] In the reaction between TcO_4^- and excess dmpe the products formed were found to depend upon the reaction conditions.[576] Initially, $[TcO_2(dmpe)_2]^+$ (**22a**) was formed which could react further to give $[Tc(dmpe)_3]^+$ or, in the presence of chloride, $[Tc(dmpe)_2Cl_2]^+$ (**22b**). Some $[TcO(dmpe)_2(OH)]^{2+}$ was also found in the reaction mixture. Such chemical effects accounted for the clinical observation that ^{99m}Tc complexes with dppe exhibited a biodistribution pattern which varied with the conditions of preparation.[577] In these examples the organophosphines used functioned as both ligand and reducing agent. Other examples of this are provided by the reactions of TcO_4^- with trispyrazoylhydroborate ($HBpz_3^-$) and with thiourea.[579] The former compound affords the octahedral Tc^V complex $[TcO(HBpz_3)Cl_2]$ while the latter affords the octahedral sulfur-coordinated Tc^{III} complex $[Tc\{S{=}C(NH_2)_2\}_6]^{3+}$.



(**22a**) R = Me, X = O
(**22b**) R = Me, X = Cl

The preceding discussion served to illustrate the potentially complicated nature of the reactions which occur when a ^{99m}Tc radiopharmaecutical is prepared by adding $^{99m}TcO_4^-$ from a generator to a 'kit' containing a complexing agent and a reductant. The situation may be further complicated if the complexing agent is impure or if other additives are present which might complex technetium. This is well illustrated by attempts to prepare a Tc^V complex of mercaptoacetic acid from $^{99}TcO_4^-$

in the presence of a reducing agent.[580] The product (**23**) of the reaction turned out to be a complex of thiomercaptoacetic acid, present as an impurity in the intended ligand. In the structure of (**23**) the Tc^{V} was found to be situated 0.79 Å above the plane defined by the four ligand sulfur atoms. Under stoichiometric conditions, complexation by such an impurity might only account for a small proportion of the technetium present. However, in a radiopharmaceutical 'kit' the complexing agent is normally present in great excess so that an impurity with a high binding constant for a particular technetium oxidation state might complex a major portion of the ^{99m}Tc present. The intended ligand might then play little or no part in determining the biodistribution of the ^{99m}Tc administered to a patient. To be effective a radiopharmaceutical should be of high radiochemical purity, that is a high proportion of the radioactivity present should be in the form specified as the desired radiopharmaceutical agent. The radiochemical purity will, of course, depend upon the purity of the radionuclide used. However, in the case of ^{99m}Tc agents it will more importantly depend upon the chemical purity of the complexing agent and upon the product distribution resulting from the reduction and complexation reactions occurring with $^{99m}TcO_4^-$. Since the clinical performance of a 'technetium essential' ^{99m}Tc radiopharmaceutical is critically dependent upon the chemical nature of the ^{99m}Tc containing species present, the measurement and control of radiochemical purity is of great importance.

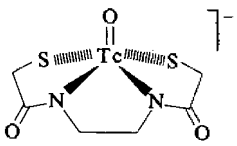


(**23**)

Until recently it has rarely been possible to definitively characterize the ^{99m}Tc species present in a radiopharmaceutical formulation because of the extremely low concentrations involved. In some cases, electrophoresis has been used as a means of determining the minimum number of species present. In a recent example a methylene diphosphonate formulation for preparing a ^{99m}Tc bone imaging agent was found to produce at least four different ^{99m}Tc species.[581] In favourable circumstances it may be possible to determine the net charge on the ionic materials present by this technique. However, such measurements require careful interpretation if erroneous conclusions are to be avoided, and they provide no detailed information relating to chemical structure.[20]

Chromatographic techniques have also been used to assess radiochemical purity on a routine basis and may be applied to both ^{99m}Tc preparations at the 10^{-6}–10^{-8} M level and ^{99}Tc complexes in the 10^{-1}–10^{-4} M concentration range. In particular, the advent of high pressure liquid chromatography, HPLC, has provided a powerful tool, both for analyzing ^{99m}Tc preparations and for relating the species present to ^{99}Tc complexes which may be isolated and characterized using conventional coordination chemistry methods. A radiometric detector may be used to monitor ^{99m}Tc in HPLC column eluates and in this way a diagnostic agent derived from (**21b**) was shown to contain two components in proportions which varied with pH.[582] The use of a dual detection system, which also incorporates a visible-UV absorbance detector, allows both ^{99m}Tc and ^{99}Tc preparations to be analyzed simultaneously on the same column. In this way, ^{99m}Tc species may be directly related to ^{99}Tc complexes on the basis of retention time. A good example of this approach is provided by the development of cationic Tc^{III} phosphine complexes (**22**) as potential heart imaging agents. HPLC analysis coupled with the characterization of model complexes of $^{99}Tc^{3+}$ has provided a basis for optimizing the conditions of preparation of the radiopharmaceutical and establishing the chemical structure of the ^{99m}Tc species involved.[583,584]

Another technique which is now being applied to both ^{99m}Tc and ^{99}Tc complexes is field desorption mass spectrometry (FDMS). In combination with HPLC this provides a direct means of obtaining chemical information about ^{99m}Tc compounds separated from a radiopharmaceutical preparation, or from biological samples obtained from a subject after administration of the radiopharmaceutical. This combination of techniques thus provides a means of assessing the *in vivo* stability of a radiopharmaceutical by identifying the species injected with those excreted or obtained by biopsy of an organ. An example of the application of this approach is provided by work[585] on the *in vivo* behaviour of the Tc^{V} complex (**24**). Measurements involving the ^{99}Tc complex at the 10^{-5} M level and carrier-free ^{99m}Tc at $<10^{-8}$ M concentrations established that virtually quantitative formation was possible from TcO_4^- at both concentrations. The ^{99}Tc complex was structurally characterized by X-ray diffraction methods and shown by HPLC and FDMS to be identical with the complex formed using $^{99m}TcO_4^-$. Studies of biological samples established



(24)

that the complex was excreted unchanged in both urine and bile and thus had high *in vivo* stability. Similar investigations of other radiopharmaceuticals should offer a greatly improved insight into both the nature and *in vivo* behaviour of ^{99m}Tc radiopharmaceuticals.

Although the exact nature of many ^{99m}Tc radiopharmaceutical formulations remains uncertain, studies of ^{99}Tc chemistry are providing an established framework of structure and reactivity patterns against which proposals regarding the ^{99m}Tc species involved may be judged. Perhaps more importantly, coordination chemistry studies with ^{99}Tc are revealing new aspects of technecium chemistry which offer great promise for the development of new radiopharmaceuticals. It is thus useful to consider those aspects of ^{99}Tc chemistry which have a bearing on the chemistry of existing ^{99m}Tc radiopharmaceuticals or on the development of new imaging agents.

Deutsch has divided the synthetic routes used to prepare technetium compounds into three categories.[20] The first of these, reduction, starts from TcO_4^- and may be applied to both ^{99m}Tc and ^{99}Tc. It involves the reduction of TcO_4^- in the presence of a large excess of a complexing agent and, as indicated above, normally gives rise to a mixture of products. This can limit the utility of the reduction route in preparing ^{99}Tc complexes since it necessitates separation of the components of the mixture before a pure compound can be isolated and characterized. However, it is the most widely used means of preparing ^{99m}Tc radiopharmaceuticals. The second category, reduction/substitution, is a special example of the first in which the technetium is complexed by a ligand which also serves as the reducing agent. This approach may be applied to a variety of technetium oxidation states and may produce more than one product. It has not been widely used for preparing ^{99m}Tc agents but can give simpler reaction product mixtures than the reduction route. Accordingly it has been of considerable value in the preparation of new ^{99}Tc complexes. The third category, substitution, involves the prior isolation of a single technetium complex which can then undergo substitution with a particular ligand to produce a specific product. This route will usually provide the simplest product mixture and is thus of great utility in the preparation of ^{99}Tc complexes. Unfortunately it is not generally suitable in clinical applications because the short half-life of ^{99m}Tc, and the limited coordination chemistry experience of most medical staff, do not allow a multistep reaction sequence to be carried out routinely in a clinical environment. However, in some cases simple, fast two-step preparative procedures are possible and might be incorporated in a kit developed for clinical use. The preparation of ^{99m}Tc gluconate or citrate complexes from $^{99m}TcO_4^-$ might provide such intermediates for use in a radiopharmaceutical formulation.

(i) Structural studies

A substantial number of ^{99}Tc complexes have now been structurally characterized[20,554] and it is likely that, to a first approximation, the majority of the ^{99m}Tc coordination geometries arising in technetium-essential radiopharmaceuticals are encompassed by these known examples. In the lower oxidation state systems containing Tc^{I} to Tc^{IV}, octahedral six-coordination is the dominant structure,[554] although the seven coordinate Tc^{III} complex $[Tc(CO)(PMe_2Ph)_3Cl_3]$ has been reported.[586] This has a distorted octahedral P_3Cl_3 coordination environment in which the P_3 face contains the remaining CO ligand. As regards the higher oxidation state complexes, no examples of Tc^{VI} complexed by an organic ligand have been structurally characterized so far. However, at present this oxidation state does not appear to be of importance in radiopharmaceutical formulations of ^{99m}Tc. The Tc^{VII} complexes TcO_4^- and Tc_2O_7 have been shown to exhibit tetrahedral four coordination,[558,559,587] while octahedral six coordination with *fac* oxo groups has been proposed[588] for $[TcO_3(L)Cl]$ (L = bipyridyl or 1,10-phenanthroline).

The dominant oxidation states in the majority of ^{99m}Tc radiopharmaceuticals used at present would appear to be Tc^{IV} and Tc^{V}. Among the structurally characterized ^{99}Tc complexes, Tc^{V} systems have also proved to exhibit the greatest degree of structural diversity. Coordination numbers ranging from 5 to 8 have been found[554] for this oxidation state and the central core units of Tc^{V} complexes may comprise Tc^{5+}, TcO^{3+} or TcO_2^+ moieties. Oligomeric species containing $Tc_2O_3^{4+}$ cores with μ-oxo or μ-hydroxo bridging ligands can also form. Some selected

Table 20 Selected Examples of Technetium(V) Complexes

Complex	*Coordination number*	*Core[a] unit*	*Ref.*
$[Tc(diars)_2Cl_4]PF_6$	8	Tc^{5+}	589
$[Tc(DMG)_3(SnCl_3)(OH)]\cdot 3H_2O$ (Figure 51)	7	$Tc^{5+}-(\mu\text{-O})$	568
Ba[TcO(EDTA)] (**25**)	7	TcO^{3+}	554
$\{[Li(H_2O)_4][Tc(MDP)(OH)]\ \frac{1}{3}H_2O\}_n$ (Figure 52)[a]	6	$Tc^{5+}-(\mu\text{-OH})$	590
$[TcO(bipy)Cl_3]$	6	TcO^{3+}	588
$[TcO(Meoxine)_2Cl]$ (**26**)[b]	6	TcO^{3+}	591
$[TcO(C_5H_{10}NO_2S)(C_5H_9NO_2S)]$ (**27**)[c]	6	TcO^{3+}	592
$[\{TcO(salpd)\}_2(\mu\text{-O})]$[d]	6	$Tc_2O_3^{4+}$	593
[TcO(salen)Cl]	6	TcO^{3+}	594
$[TcO(HBpz_3)Cl_2]$	6	TcO^{3+}	578
$[TcO(H_2O)(acac_2en)]\cdot\frac{1}{4}Cl\cdot\frac{3}{4}Br$[e]	6	TcO^{3+}	594
$[TcO_2(en)_2]I$	6	TcO_2^+	595
$[TcO_2(cyclam)]ClO_4\cdot H_2O$ (**30**)[f]	6	TcO_2^+	596
$[TcN(PMe_2Ph)_3Cl_2]$	6	TcN^{2+}	597
$Ph_4As[TcO(SCH_2CH_2S)_2]$	5	TcO^{3+}	598
$Bu_4N[TcO(SCH_2C(O)S)_2]$ (**23**)	5	TcO^{3+}	580
$Ph_4As[TcO(SCH_2CH_2O)_2]$	5	TcO^{3+}	599
[TcO(salOPh)Cl] (**28**)[g]	5	TcO^{3+}	600
$MePh_3As[TcO(ema)]$ (**24**)[h]	5	TcO^{3+}	581
$[TcN(Et_2dtc)_2]$ (**29**)	5	TcN^{2+}	575

[a] MDP = methylenediphosphonate.
[b] Meoxine = 2-methyl-8-hydroxyquinoline.
[c] $C_5H_{10}NO_2SH$ = D-penicillamine.
[d] salpd = *N*,*N*′-propane-1,3-diylbis(salicylideniminate).
[e] $acac_2en$ = *N*,*N*′-ethylenebis(acetylacetoniminate).
[f] cyclam = 1,5,8,12-tetraazacyclotetradecane.
[g] $salOPhH_2$ = 2-hydroxyaniline-*N*-salicylaldimine.
[h] $emaH_2$ = *N*,*N*′-ethylenebis(2-mercaptoacetamide).

examples of Tc^V complexes are listed in Table 20 to illustrate this structural diversity. Although an isolated example at present, the dodecahedral D_{2d} geometry found[589] in $[Tc(diars)_2Cl_4]^+$ does establish the ability of the Tc^{5+} core to accept eight coordination. The TcO^{3+} core has been shown to accept at least six additional ligating atoms, as demonstrated[20] by $[TcO(EDTA)]^-$ (**25**). The Tc^V centre was found to have a distorted pentagonal bipyramidal coordination environment in which the oxo group and the two nitrogen atoms occupied equatorial positions. The dinuclear system $[Tc(DMG)_3(SnCl_3)(OH)]$ also contained seven-coordinate Tc^V,[569] but in addition demonstrated the ability of the technyl oxo group to become involved in bonding to a second metal centre (Figure 51). Such behaviour is relevant, not only to the incorporation of tin into ^{99m}Tc radiopharmaceutical agents, but also to the possible binding of ^{99m}Tc complexes to sites containing Ca^{2+} in bone. In this context a structural study of a ^{99}Tc complex formed from methylene diphosphonate (MDP), which is used with ^{99m}Tc as a bone scanning agent, has revealed a polymeric structure involving μ-OH groups bridging Tc^V centres.[590] The MDP ligands also bridge between Tc^V centres and are in turn linked by bridging Tc^V groups, as shown in Figure 52. Although

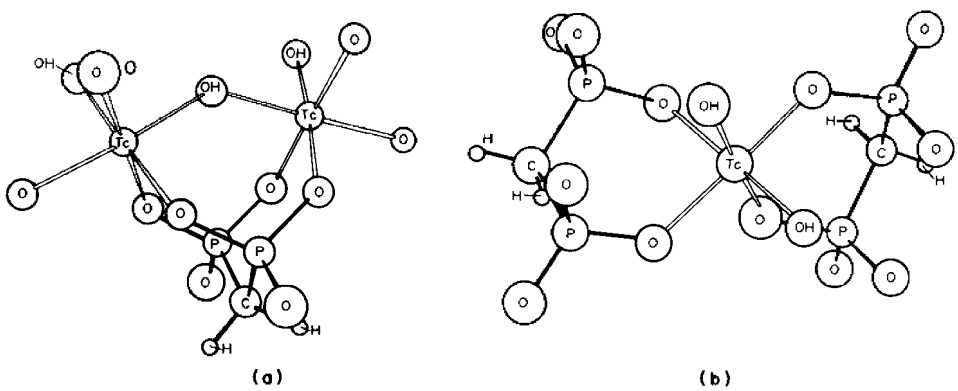
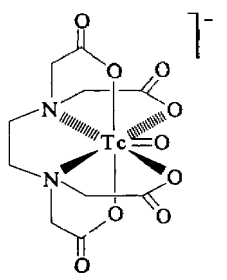
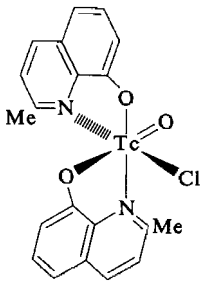


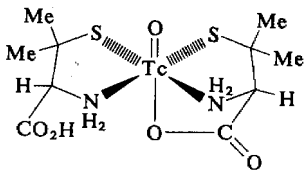
Figure 52 The structures of the $[Li(H_2O)_3][Tc(OH)(MDP)]\cdot\frac{1}{3}H_2O$ polymer showing (a) an MDP ligand bridging two Tc centres and (b) a Tc centre bridging two MDP ligands. (Reproduced from E. Deutsch and B. L. Barnett, *ACS Symp. Ser.*, 1980, **140**, 103, with permission from the American Chemical Society)



(25)



(26)

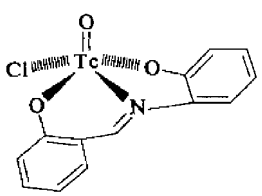


(27)

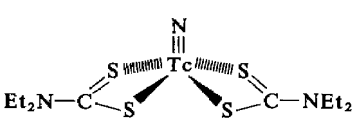
$\{Tc(MDP)OH\}_n^{n-}$ was prepared by a different means from that used for the ^{99m}Tc bone scanning agent, and was only one of several products formed, its structure does provide a detailed insight into possible ^{99m}Tc-MDP binding modes.

Among six-coordinate Tc^V complexes containing a TcO^{3+} core unit, the strong *trans* effect of the oxo group is a common structural feature. In $[TcO(Meoxine)_2Cl]$ (**26**), for example, the Tc—O bond distances *cis* and *trans* to the oxo group are 1.95 and 1.99 Å respectively.[591] A similar situation arises in the complex $[TcO(HBpz_3)Cl_2]$, in which the tripodal ligand is obliged to bind facially to the TcO^{3+} group.[578] The Tc—N distance *trans* to the oxo group was found to be 2.26 Å compared with 2.09 Å for those *cis* to the oxo group and *trans* to chlorine. In situations where different donor atom types are present in a ligand there is a tendency for oxygen or chloride to be preferred as the atom *trans* to the oxo group in six-coordinate complexes. An example of this is provided by the D-penicillamine complex (**27**), in which the S atoms are mutually *cis*, as are the N atoms, while a carboxyl group on one of the ligands is protonated and not coordinated.[592] In [TcO(salen)Cl], where the planar ligand geometry favours oxygen binding *cis* to the oxo group, it is chloride which binds in the *trans* position.[594]

The *trans* influence of the oxo group in Tc^V complexes containing the TcO^{3+} core leads to increased lability for ligands bound in the *trans* position. In the extreme this results in square pyramidal five-coordination and many examples of such species are known.[554] A common structural feature in these compounds is the displacement of the Tc^V ion out of the plane of the four basal ligands towards the apical oxo group. In the series $[TcOL_2]^-$, where $L = SCH_2CH_2S$,[598] $SCH_2C(O)S$ (**23**)[580] and SCH_2CH_2O,[599] for example, the Tc^V ion was found to lie between 0.76 and 0.79 Å above the basal plane. Similar effects have been found in Tc^V complexes containing tri- and tetra-dentate ligands. In [TcO(salOPh)Cl] (**28**), prepared as a model for pyridoxylidenamine hepatabiliary imaging agents,[600] the value was 0.67 Å, and in $[TcO(ema)]^-$ (**24**) it was 0.77 Å.[581] The displacement of the Tc^V ion from the basal plane has also been observed in the structures of Tc^V complexes containing the $Tc{\equiv}N^{2+}$ core. In $[TcN(Et_2dtc)]$ (**29**), for example, the Tc^V ion was located 0.75 Å above the basal plane. Another feature present in the structure of (**23**) was the *cis* arrangement of the thiolate sulfur atoms. Although both *cis* and *trans* isomers were detected during the preparation of this material from $[TcOCl_4]^-$, only the *cis* complex could be isolated in pure form. This cisoid arrangement of thiolate groups is also found in $[TcO(SCH_2CH_2O)_2]^-$ and in (**27**) and may reflect a genuine preference for this arrangement in such five-coordinate complexes of Tc^V.



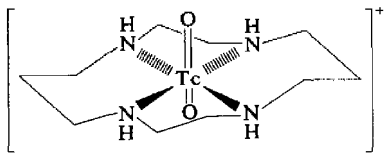
(28)



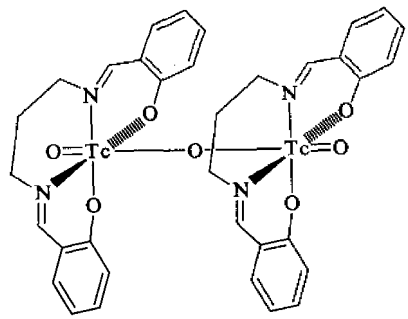
(29)

When ligands containing only nitrogen donor atoms are used to prepare Tc^V complexes there is a tendency to retain a second oxygen on the technetium in the form of a TcO_2^+ core unit. This has been rationalized[20] in terms of the failure of neutral nitrogen donors to neutralize charge on the Tc^V core effectively. Thus, where neutral ligands only are present, a second oxo group is retained to optimize electroneutrality at the metal. The π-acidity of the in-plane ligand set may also be important in determining whether the second oxo group is retained. Thus $[TcO_2(CN)_4]^{3-}$forms[601] because the π-acid nature of the cyanide offsets the effects of its negative

charge. Several cationic six-coordinate complexes containing the TcO_2^+ core have been reported,[20] among which $[TcO_2(en)_2]^+$ and $[TcO_2(cyclam)_2]^+$ have been structurally characterized and are of importance in the context of nuclear medicine. The latter complex[596] adopts the structure (**30**) containing the *trans* dioxo TcO_2^+ core, as do the related complexes with other neutral nitrogen donors.[20,595] Derivatives of cyclam carrying alkyl or aryl substituents have been used to complex ^{99m}Tc and were then evaluated as potential myocardial imaging agents.[602] They were presumed to be structurally analogous to (**30**) but failed to show myocardial uptake.

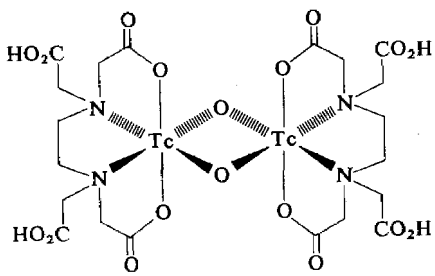


(**30**)

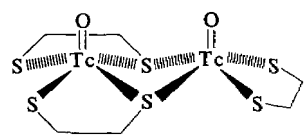


(**31**)

In addition to compounds containing the TcO^{3+} or TcO_2^+ cores, examples of dinuclear Tc^V complexes containing the linear $O{=}Tc{-}Tc{=}O^{4+}$ core are also known. This geometry has been established[593] in $[\{TcO(salpd)\}_2(\mu\text{-}O)]$ (**31**) and is proposed[552] for $[\{TcO(Et_2dtc)_2\}_2(\mu\text{-}O]$. In contrast, bent oxo-bridged structures have been found in the dinuclear Tc^{IV} complexes $[\{Tc(\mu\text{-}O)(NTA)\}_2]\cdot 6H_2O$ (**20**)[567] and $[\{Tc(\mu\text{-}O)(EDTAH_2)\}_2]\cdot 5H_2O$ (**32**),[603] which contain the $Tc_2O_2^{4+}$ core. A dinuclear Tc^V complex which contains thiolate bridging groups has been reported.[604] This complex, $[\{TcO(edt)_2\}TcO(edt)]$ (**33**), was formed[605] from the reaction between ethane-1,2-dithiol ($edtH_2$) and $TcOCl_4^-$. However, the bridging arrangement was disrupted in the presence of excess ligand to give only $[TcO(edt)_2]^-$. Examples of structurally characterized polynuclear complexes of technetium in oxidation states below (IV) are presently restricted to compounds containing Tc—Tc bonds.[20,534] These are formed under conditions which are inappropriate for the preparation of ^{99m}Tc radiopharmaceuticals and, on the basis of current knowledge, oligomerization would not seem to be important in low oxidation state ^{99m}Tc radiopharmaceutical formulations.



(**32**)



(**33**)

Among the known lower oxidation state complexes of ^{99}Tc, those which have a major bearing on current developments in radiopharmacy may be divided into two broad categories. The first contains homoleptic complexes of general formula $[TcL_6]^z$ in which $z = +3$ and L = thiourea (tu)[579] or tetramethylthiourea (tmtu)[606] or $z = +1$ and L = alkyl or aryl isocyanide[607] or trialkyl phosphite.[606] The tu and tmtu complexes do not appear to have medical application in their own right. However, they do represent conveniently prepared intermediates which provide a potentially important route to low oxidation state technetium complexes which do have potential medical applications.[606] The second category contains heteroleptic complexes of general formula $[Tc(L{-}L)_2X_2]^z$ in which L—L is a bidentate ditertiary phosphine[20,583,608,609] or arsine[20,610–612] ligand, X is halide and z is +1 or 0.[20,609] Complexes containing only halide and tertiary phosphine or arsine ligands are known[20] for technetium in oxidation states ranging from (II) to (V), but it is only the oxidation state (III) species which have shown promise in the context of nuclear medicine.[613,614] All of these complexes contain six coordinate technetium centres which have an

octahedral coordination geometry. The thiourea complexes are sulfur bonded while the phosphine and arsine complexes contain halide ligands in a *trans* arrangement.

(ii) Chemical studies

The majority of synthesis and reactivity studies which have been carried out on ^{99}Tc complexes have been conducted under conditions far removed from those prevailing during the preparation of a ^{99m}Tc radiopharmaceutical agent. Consequently, they do not offer information which relates directly to the mechanism of formation of ^{99m}Tc complexes from $^{99m}TcO_4^-$. Furthermore, the details of the ^{99m}Tc reduction-complexation mechanism will vary depending upon the reductant, complexing agent and reaction conditions employed. In spite of this, studies involving ^{99}Tc complexes have revealed a number of basic features in the coordination chemistry of technetium which are of relevance to the preparation of ^{99m}Tc compounds. Thus the isolation[588] of $[TcO_3(L{-}L)Cl]$ (L—L = bipy, *o*-phen) establishes that Tc^{VII} coordination complexes containing the TcO_3^+ core can form. However, the absence[20] of any examples of Tc^{VI} complexes containing organic ligands and Tc=O groups suggests that such species may be too reactive to appear in the products of a preparation involving TcO_4^- reduction. The reduction reactions of TcO_4^- involve the removal of oxygen ligands and reactions such as (216) and (217), in which L_n and 'L' are unspecified ligands and PR_3 is a tertiary phosphine, can be proposed to rationalize this. The

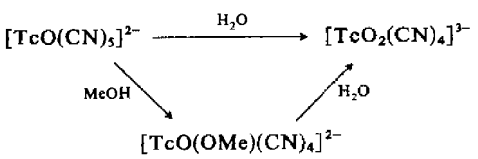
$$2L' + L_nTc^{V}O + Sn^{II} \rightarrow L_nTc^{III}L'_2 + OSn^{IV} \quad (216)$$

$$3PR_3 + L_nTc^{V}O \rightarrow L_nTc^{III}(PR_3)_2 + R_3PO \quad (217)$$

ability of tertiary phosphines to abstract oxygen is well established and reactions such as (217) are implicated in the formation[576] of $[Tc(dmpe)_2Cl_2]^+$ from TcO_4^- and excess dmpe by the observation of the reaction intermediate $[TcO_2(dmpe)_2]^+$. However, in aqueous media, protonation equilibria such as (218) will also be involved. The importance of protons in determining the outcome of a reaction is illustrated by attempts to prepare $[TcO(edt)_2]^-$ from TcO_4^- using $S_2O_4^{2-}$ as the reductant.[555] The reaction was successful when the dithiol, $edtH_2$, was used but afforded only TcO_2 when the salt, $edtNa_2$, was used.

$$L_nTcO_2^+ + 2H^+ \rightleftharpoons L_nTcO(H_2O)^{3+} \quad (218)$$

Whether a reduction producing a Tc^V complex gives rise to a compound with a TcO^{3+} or a TcO_2^+ core will depend upon the nature of the ligand set involved. Soft ligands such as thiolate, and anions which are not π-acids, stabilize the TcO^{3+} core, but π-acid or hard neutral ligands stabilize the TcO_2^+ core. Thus the reaction of $[TcOCl_4]^-$ with dithiooxalate afforded[555] $[TcO(C_2O_2S_2)_2]^-$ but $[TcO_2(C_5H_5N)_4]^+$ was formed with pyridine.[21] Another example of the conversion of the TcO^{3+} core to TcO_2^+ is provided[601] by the methanolysis and hydrolysis of $[TcO(CN)_5]^{2-}$, as shown in Scheme 10. Table 21 summarizes some observations on the relationship

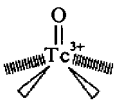
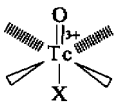
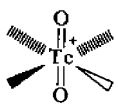
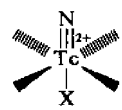


Scheme 10

between the ligand donor atom set and the type of Tc^V complex which is isolated. Some Tc^V complexes containing the TcN^{2+} core are also included for comparison. The nature of the ligand set will also affect the stability of a Tc^V complex in aqueous media. Hard ligands are labile and prone to ligand exchange or hydrolysis reactions while soft ligands, such as dithiolate, give inert complexes containing the TcO^{3+} core. Examples of this are provided by the water stable complex $[TcO(edt)_2]^-$ and by $[TcOCl_4]^-$, which rapidly hydrolyzes in water.

Another illustration of this point is provided by the exchange reactions of $[TcO(L{-}L)_2]^-$ (L—L = OCH_2CH_2O, OCH_2CH_2S or $SCH_2CH_2CH_2S$) with $edtH_2$, in which the rate of substitution

Table 21 Effect of Donor Atom Set on Tc^{V} Complex Type

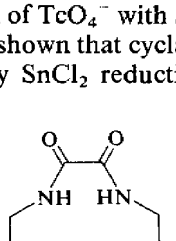
Technetium core type	*Donor atom set*		*Example*	*Ref.*
	$(S^-)_4$		$[TcO(edt)_2]^-$	555, 598, 619
	$(S^-)_4$		$[TcO\{SCH_2C(O)S\}_2]^-$	580
	$(S^-)_2(O^-)_2$		$[TcO(OCH_2CH_2S)_2]^-$	599
	$(O^-)_4$		$[TcO(OCH_2CH_2O)_2]^-$	616
	$(S^-)_2(N^-)_2$		[TcO(ema)]$^-$	617
	$(O^-)_2NCl^-$		[TcO(salOPh)Cl]	600
	$(Cl^-)_4$		$[TcOCl_4]^-$	620, 621
	$(Br^-)_4$		$[TcOBr_4]^-$	620, 621
	*X*			
	$O^{=}$	$(S^-)_2N_2$	$[TcO(C_5H_{10}NO_2S)_2H]$	592
	Cl^-	$(O^-)_2N_2$	[TcO(salen)Cl]	594
	OH_2	$(O^-)_2N_2$	$[TcO(acac_2en)(OH_2)]^+$	594
	$(\mu O)^-$	$(O^-)_2N_2$	$[\{TcO(salpd)\}_2(\mu\text{-}O)]$	593
	O^-	$O^-N_2Cl^-$	$[TcO(Meoxine)_2Cl]$	591
	$(OH)^-$	P_4	$[TcO(dmpe)_2(OH)]^{2+}$	576
	$(CN)^-$	$(CN^-)_4$	$[TcO(CN)_5]^{2-}$	601
	$(OMe)^-$	$(CN^-)_4$	$[TcO(CN)_4(OMe)]^{2-}$	601
	$(O^-)_2$	$(O^-)_2N_2$	[TcO(EDTA)]$^-$	20
	N_4		$[TcO_2(cyclam)]^+$	596
	N_4		$[TcO_2(en)_2]^+$	595
	N_4		$[TcO_2(pyridine)_2]^+$	622
	P_4		$[TcO_2(dmpe)_2]^+$	576
	$(CN^-)_4$		$[TcO_2(CN)_4]^{3-}$	601
	$(S^-)_2S_2$		$[TcN(Et_2dtc)_2]$	575
	$(S^-)_2N_2$		[TcN(ipctc)$_2$][a]	623
	P_4		$[TcN(dppe)_2]^{2+}$	623
	$(Cl^-)_2P_2$		$[TcN(PPh_3)_2Cl_2]$	597
	*X*			
	(MeCN)	$P_2(N^-)_2$	$[TcN(PPh_3)_2(MeCN)(NCS)_2]$	624
	PPh_3	$(Cl^-)_2P_2$	$[TcN(PPh_3)_3Cl_2]$	597

[a] ipctc = 2-*N*-isopropylaminocyclopent-1-ene-1-dithiocarboxylate.

$$L{-}L = OCH_2CH_2O > SCH_2CH_2O \gg SCH_2CH_2CH_2S$$

Scheme 11

of L—L was found[615] to follow the order in Scheme 11. The reaction with $L{-}L = OCH_2CH_2O$ was almost instantaneous but when $L{-}L = SCH_2CH_2CH_2S$ it was necessary to add acid to stimulate the ligand exchange. Reactions such as these indicate that Tc^{V} citrate or glucoheptonate complexes, which are presumably structurally related to $[TcO(OCH_2CH_2CH_2O)_2]^-$, might be useful intermediates in the preparation of more stable Tc^{V} complexes. In fact, Davison and coworkers have used $[TcO(OCH_2CH_2O)_2]^-$ as a convenient reagent for preparing[616] Tc^{V} complexes of tetradentate ligands such as (**34**). The reaction products were structurally related to (**24**), which was prepared previously by the reduction of TcO_4^- with $S_2O_4^{2-}$ in the presence of the tetradentate ligand.[617] Studies[618] with ^{99m}Tc have also shown that cyclam can strip technetium from its complex with citrate. This had been prepared by $SnCl_2$ reduction of $^{99m}TcO_4^-$ in the presence of the carboxylate ligand.



(**34**)

In non-aqueous media the d^3 Tc^{IV} centre appears to be relatively kinetically inert,[20] so that substitution reactions of $[TcCl_6]^{2-}$ are slow compared with those of $[TcOCl_4]^-$. However, in aqueous media, hydrolysis of Tc^{IV} can occur and $[TcCl_6]^{2-}$ is rapidly converted to TcO_2. Polyden-

tate carboxylate ligands appear able to suppress the hydrolysis reactions but it is interesting to note that the structurally characterized examples of Tc^{IV} complexes with NTA[567] and EDTA[603] are dimeric and contain bridging oxo ligands, Oligomerization reactions would appear to be important in this class of compound and may partly account for the observation of more than one product when $^{99m}TcO_4^-$ is reduced in the presence of amine carboxylate ligands.

In order for oxidation states below Tc^{IV} to be stable in aqueous media, complexation by π-acids ligands appears essential[20,552]. The reduction of TcO_4^- to Tc^{III} may be effected using Sn^{II},[20] thiols,[20] thiourea[579] or tertiary phosphines,[20,625] although Tc^{IV} complexes were formed with PPh_3 in HCl.[626] A structural study[627] of $[Tc(NCS)_6]^{3-}$ has revealed a Tc—N distance of 2.04 Å, almost identical with the 2.05 Å figure for the analogous Fe^{III} complex.[628] The implications of this are that Tc^{III} might be substituted for Fe^{III} in biological systems.[21] However, to exploit this feature of technetium chemistry it will be necessary to prevent hydrolysis reactions from competing with the biological host for Tc^{III}.

Electrochemical studies[20,629] of the chelating phosphine complexes of Tc^{III}, $[Tc(L—L)X_2]^+$, where L—L is a chelating ditertiary phosphine or arsine and X = halogen, have revealed a well defined reduction process corresponding with the Tc^{III}/Tc^{II} couple, but no oxidation processes were observed. The effect of variations in the nature of L—L of X on the reduction potentials of the complexes were examined. The major influences were found to be the nature of X and whether L—L carried alkyl or aryl substituents. Thus changing from Cl^- to Br^-, or from dmpe to dppe, facilitated the reduction reaction. The reduction potentials were found to be within the range accessible to biological systems, suggesting that the reduced species $[Tc(L—L)X_2]$ might play a role in determining the biodistribution behaviour of ^{99m}Tc imaging agents based on such systems. Changing X from halide to NCS stabilized the Tc^{II} oxidation state so that the octahedral complex *trans*-$[Tc(dppe)_2(NCS)_2]$ could be isolated in this case.[630] Cyclic voltammetric studies of this compound revealed two waves corresponding with the $Tc^{II/III}$ oxidation and $Tc^{II/I}$ reduction processes. The $Tc^{II/I}$ couple was also observed in the complexes in which X = halide, but was irreversible.

As with these monocationic Tc^{III} species, the Tc^{I} complexes $[TcL_6]^+$ (L = trialkyl phosphite or alkyl isocyanide) have aroused interest as potential myocardial imaging agents. The chemical reduction of TcO_4^- to Tc^{I} by $P(OMe)_3$ requires rather forcing conditions.[631] However, $[Tc\{P(OMe)_3\}_6]^+$ is readily prepared from $[Tc(tu)_6]^{3+}$ and excess $P(OMe)_3$. Since $[Tc(tu)_6]^{3+}$ may be prepared directly from TcO_4^- and thiourea,[579] the Tc^{I} phosphite complex may thus be prepared from TcO_4^- under mild conditions using a two-step reaction sequence. The Tc^{I} isocyanide complex, $[Tc(Bu^tNC)_6]^+$, may also be conveniently prepared from $^{99m}TcO_4^-$ by reacting a standard preparation of ^{99m}Tc glucoheptonate with the Bu^tNC adduct of $ZnBr_2$. Thus even Tc^{I} species are obtainable from TcO_4^- under conditions which are not precluded by the requirements of a clinical environment.

Recently the Tc^{VI} species $[TcNX_4]^-$ (X = Cl, Br) have been prepared from the reaction of N_3^- and TcO_4^- in concentrated HX solution. They were shown to have a square pyramidal structure with an apical nitride.[633] Substitution reactions of $[^{99m}TcNCl_4]^-$ preparations with MDP, DTPA and cysteine have been used to prepare new agents for clinical evaluation. Although radiochemically pure products could be obtained, these radiopharmaceuticals did not prove to be of clinical use. However, their behaviour was different from that of analogous preparations containing TcO^{3+} instead of TcN^{3+} and further studies with this system would seem to be warranted. This development demonstrates that, in principle, all seven technetium oxidation states, from Tc^{I} to Tc^{VII}, are available for medical use. Although the clinical utility of the oxidation state (II) and (VI) complexes has yet to be established, it may be presumed that, when suitable complexing agents are identified, these two will find a role and further extend the range of clinical applications of ^{99m}Tc.

Radiopharmaceutical formulations based on ^{99m}Tc may be divided into two major classes.[635] The Class I formulations include what may be described as technetium tagged materials. These may be particles such as cells or colloidal substances, or they may be molecular species such as proteins or other large biological molecules. The essential feature of these agents is that their biodistribution behaviour is determined by the nature of the substrate material. Thus the attachment of a ^{99m}Tc label should have little or no effect on their biodistribution. However, it cannot necessarily be assumed that this will be the case, especially when relatively low molecular weight substrates are involved.

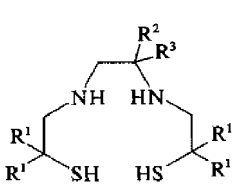
The Class II formulations are the so called 'technetium essential' radiopharmaceuticals whose biodistribution depends not only on the nature of the substrate to be labelled, but also on the presence of ^{99m}Tc itself. Some examples of the major types of ^{99m}Tc radiopharmaceutical agents in use, or under investigation, are summarized in Table 22. The nature of the ^{99m}Tc binding site

Table 22 Examples of ^{99m}Tc Radiopharmaceuticals

Application	*Class*[a]	*Principle*	*Formulation*[b]	*Ref.*
Blood pool imaging	I	Distribution of labelled blood cells	Citrate + cells	636
			Oxine + cells	637
			Sn^{2+} only + cells	638
Lymph system imaging	I	Liposome uptake in lymph nodes affected by tumor	TcO_4^-/Sn^{2+} incorporated in phospholipid vesicle	639
Stomach imaging	I	Suspension of particles in stomach	Reaction of TcO_4^- with polymer beads treated with triethylenetetramine*	640
			TcO_4^- adsorbed on ion exchange resin beads*	641
Liver and spleen structure studies	I	Trapping in reticulo-endothelial system	Colloidal Tc_2S_7 preparation from $TcO_4^- + H_2S$	551, 642
Spleen imaging	II	Damaged blood cell uptake by spleen	Denatured ^{99m}Tc labelled red blood cells	505
Lung scanning	I	Trapping of microspheres in capilliaries	Albumin microspheres	643
Thyroid scanning	II	Reversible anion uptake	TcO_4^-*	551
Bone scanning	II	Binding of phosphonate to bone surface or Tc exchange with hydroxyapatite	MDP or hydroxyethane-1,1-diphosphonate (HEDP)	20, 553, 644, 645
Liver and bile duct function studies	II	Transport through hepatocytes to bile duct	Carbamoyliminodiacetate derivatives (**21**)	20, 551, 553
Kidney function studies	II	Glomerular filtration and distribution in extracellular fluid	DTPA	553, 646, 647
Kidney structure studies	II	Binding in kidney cortex	Dimercaptosuccinic acid or glucoheptonate	20, 553, 647
Myocardial imaging under development	II	Cation uptake in myocardium	Chelating ditertiary phosphine or arsine (**22**)	20, 613, 614
			Alkyl isonitrite	607
Brain scanning	II	Accumulation at tumor disrupted sites	TcO_4^-*	551
			Glucoheptonate	505
Brain scanning experimental studies	II	Diffusion through blood/brain barrier	Bis-*N,N'*-(2-thioethyl)ethylenediamine derivatives (**35**)	648, 649

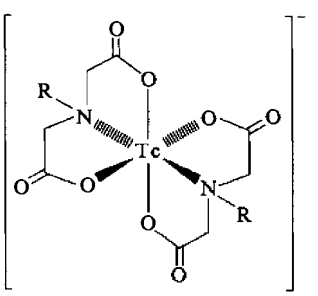
[a] Class I are 'tagged materials', Class II are 'technetium essential' systems.
[b] Formulations normally incorporate a reducing agent such as $SnCl_2$ unless marked*. Other additives may also be present: ascorbic acid, for example, is sometimes incorporated as an antioxidant.

in most Class I radiopharmaceuticals remains unknown. However, the more recently developed Class II agents, such as those derived from dmpe, Bu^tNC and (**35**), are based on known ^{99}Tc chemistry so that the nature of the ^{99m}Tc species involved is well established. On the basis of known ^{99}Tc chemistry it might also be presumed that the most stable $^{99m}Tc^V$ complex of dimercaptosuccinic acid (DMSA) would be structurally related to $[TcO(edt)_2]^-$. The nature of the complexes formed between ^{99m}Tc and MDP or hydroxyethane-1,1-diphosphonate (HEDP) is less certain, but a ^{99}Tc model again exists to illustrate one possible binding mode, as shown in Figure 52. Although several ^{99}Tc complexes of amine-carboxylate ligands have now been structurally characterized, the nature of the ^{99m}Tc complexes formed with DTPA or the hepatobiliary agents (**21**) has not been conclusively determined. Structure (**36**) has been proposed[650] for the complex of



(**35**)

R^1	R^2	R^3
Me	Me	Me
Me	H	H
Et	H	H
Me	H	CH_2OH
Me	H	CH_2NH_2
Me	H	*o*-C_6H_4OH
Et	H	C_6H_{11}



(**36**)

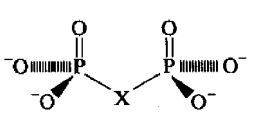
^{99m}Tc with (**21**) based on electrophoresis studies[635] which showed the complex to be monoanionic and to have a ligand/metal ratio of 2:1. However, such a structure would not be in accord with the observed need for π-acid ligands to stabilize Tc^{III} in aqueous media. A more realistic proposal[20] might be based on a 2:1 ligand complex of a TcO^{3+} core. This would give a seven-coordinate Tc^{V} structure, as has been found in $[TcO(EDTA)]^-$.

As yet, the detailed relationship between structure and biodistribution in ^{99m}Tc radiopharmaceuticals is not well understood. Furthermore, experiments designed to reveal such relationships must take account of the fact that a ^{99m}Tc formulation will usually produce more than one ^{99m}Tc complex, and that the exact nature of the complexes present may be unknown. Despite this, certain general observations may be made, for example hydrophilic complexes are primarily cleared from the blood by renal excretion while lipophilic complexes are primarily excreted through the hepatobiliary system.[635] It is also apparent that lipophilic monocationic complexes can accumulate in the myocardium.[20,607] However, the presence of oxo groups appears to eliminate this property, as found[602] for the derivatives of $[^{99m}TcO_2(cyclam)]^+$. Lipophilic complexes such as those derived from ^{99m}Tc and (**35**) can cross the blood/brain barrier.[648,649] However, to be effective as brain imaging agents, longer in-brain retention times would be needed. At a more detailed level, a linear relationship between the proportion of biliary excretion and the logarithm of the molecular weight to charge ratio has been found[651] for ^{99m}Tc-iminodiacetate complexes formed from substituted derivatives of (**21**). However, as pointed out above, the structure (**36**) assumed for these complexes does not appear chemically reasonable and HPLC studies[582,652] show that more than one complex is present. As regards the performance of existing ^{99m}Tc radiopharmaceutical formulations, very effective agents are now available for bone, liver and kidney scanning. Thus the major thrust of future research in this area is likely to be towards new diagnostic agents for heart, brain and tumor studies, and already agents which show great promise for myocardial imaging are emerging. Such developments demonstrate that studies of the coordination chemistry of ^{99}Tc are not only shedding light on the nature of existing agents, but also leading the search for new types of ^{99m}Tc radiopharmaceuticals.

65.3.2 Diagnostic Imaging Applications of Radiopharmaceuticals

65.3.2.1 Bone

Reviews of bone scanning agents have been provided by Merrick[644] and, more recently, by Brill.[653] Early formulations incorporated ^{18}F or strontium isotopes. However, the utility of ^{18}F has been limited by its short half-life and the need for on- or near-site cyclotron generation, while ^{87m}Sr was found to give a high background radiation due to soft tissue uptake. Better target/background radiation ratios were obtained with ^{85}Sr, but at the expense of high patient radiation doses.[644] A variety of alternative agents were investigated and ^{99m}Tc complexes with pyrophosphate, *e.g.* (**37a**), or polyphosphate were found to be effective for bone scanning. These agents were, in turn, superseded by ^{99m}Tc-diphosphonate formulations,[645] among which ^{99m}Tc-MDP gave superior images because of its faster clearance from the blood.[654] Some examples of bone scans obtained using ^{99m}Tc-MDP are presented in Figure 53. Studies of the relationship between structure and biodistribution for ^{99m}Tc-phosphonate systems have indicated that only one phosphonate group is necessary for bone uptake to occur.[553] In the series of ligands $RP(=O)O_2^-$, those in which the substituent R, in combination with a $P—O^-$ moiety, could form a five- or six-membered chelate ring on technetium showed the highest degree of bond localization.[655] Examples of such systems were provided by reagents in which $R = CH_2CO_2H$ or $OC(=O)NH_2$. The substituted diphosphonates HMDP (**37c**) and HEDP (**37d**) have also been studied[656] and their complexes with ^{99m}Tc appeared to show greater uptake in metabolically active bone than ^{99m}Tc-MDP.[553] This could offer greater contrast between normal bone and regions of abnormal metabolism such as tumor sites. The replacement of the phosphorus atoms in MDP by arsenic did not lead to any significant changes in bone uptake.[657]



(**37a**) X = O, PYP
(**37b**) X = CH_2, MDP
(**37c**) X = CH(OH), HMDP
(**37d**) X = C(OH)Me, HEDP

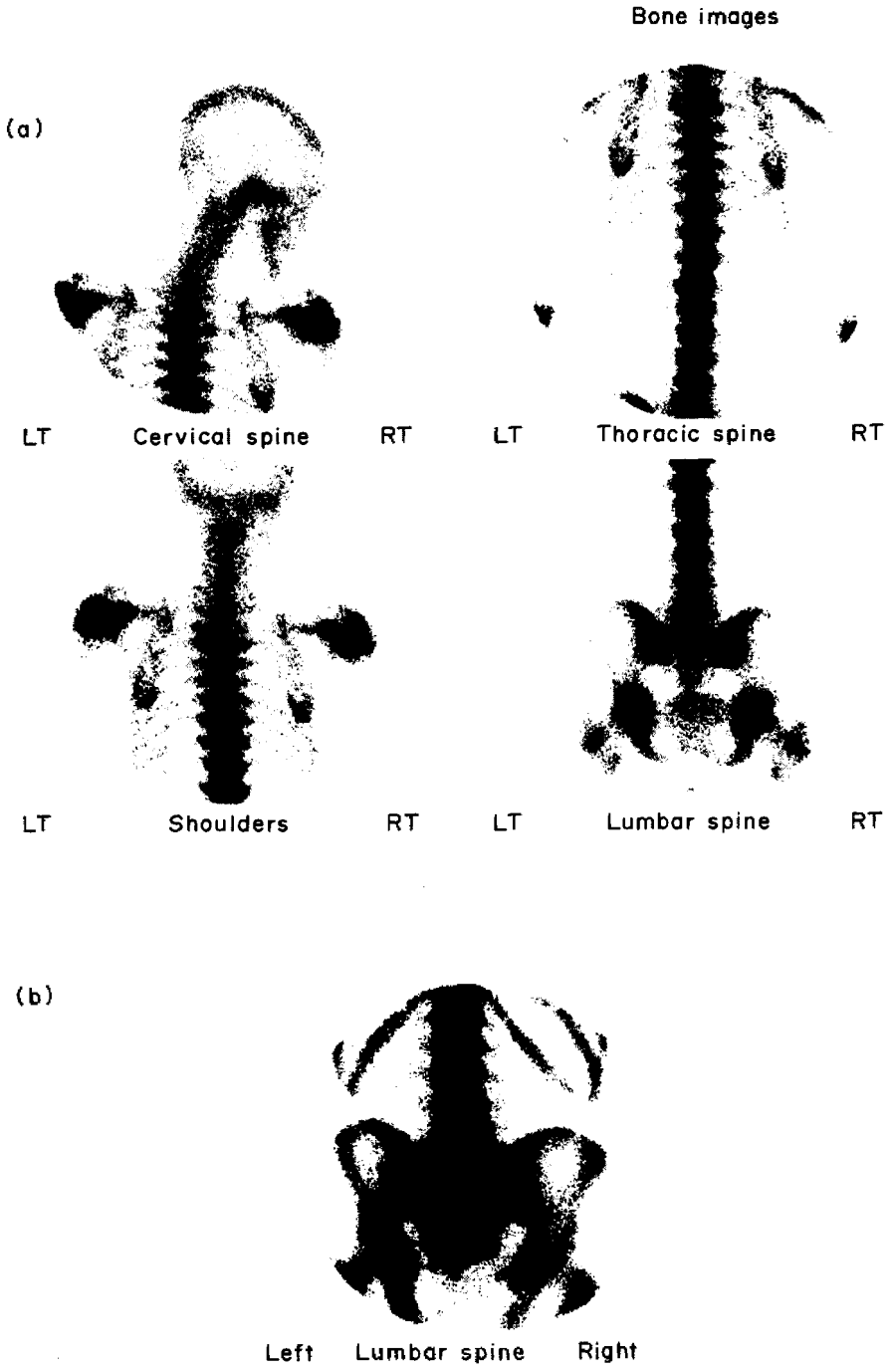


Figure 53 Bone images obtained using ^{99m}Tc-MDP showing (a) normal skeleton and (b) high ^{99m}Tc uptake due to bone disease. (Courtesy of the Nuclear Medicine Department, Queen Elizabeth Hospital, Birmingham, UK)

Analytical studies of ^{99m}Tc bone scanning formulations have shown that several complexes may be present.[20,553,551] In the case of ^{99m}Tc-PYP, two components with charges in the range −9 to −12 were detected by ion exchange chromatography, and were presumed to be polynuclear complexes.[658] Electrophoretic studies of a ^{99m}Tc-MDP formulation showed that at least four components were present, and that MDP hydrolysis to PO_4^{3-} and methyl phosphate gave rise to ^{99m}Tc species with poor bone imaging properties.[581] The use of Sn^{II} as a reducing agent for $^{99m}TcO_4^-$ in these formulations may complicate the product distributions obtained, since Sn^{IV} and Tc^{IV} can form similar complexes and Sn^{IV} might replace $^{99m}Tc^{IV}$ in some of the binding sites in polynuclear species. This possibility does not arise when BH_4^- is used as the reductant and

the components of a ^{99m}Tc-$NaBH_4$-HEDP formulation have been studied using anion exchange HPLC.[20,659] Under carrier-added conditions with a 3×10^{-3} M ^{99}Tc concentration, oligomerization occurred giving rise to at least seven different complexes. However, in the carrier-free ^{99m}Tc system, polymer formation was not favoured and one product predominated. The biodistribution behaviour of the individual carrier-added formulation components was studied and it was found that the complexes of lowest retention time, and thus lowest negative charge density, gave the largest bone uptake, lowest kidney uptake and fastest blood clearance.[659] These results provide a basis for improving the formulation of ^{99m}Tc-diphosphonate bone agents to optimize the yield of the complex having the most desirable biodistribution behavior. They also indicate that studies of biodistribution which do not take account of differences in the biological behaviour of the various components present in the formulation used, may reach misleading conclusions.

A major application of bone scanning agents is in the diagnosis of occult metastatic disease.[644] The mechanisms by which ^{99m}Tc-diphosphonate agents selectively accumulate at sites of newly forming or cancerous bone are not fully understood. Any of several mechanisms might be involved including adherence to denatured protein, binding to soft tissue iron deposits, binding to calcium complexes within the cells of infarcted tissues and extracellular metastatic calcification during hypercalcemia.[653] The increased blood supply to cancerous or injured bone may also play a role. The diphosphonate agents exhibit a high affinity for calcium, even after they have formed a complex with technetium, and this is undoubtedly an important chemical basis for their uptake by bone. That this behaviour is not determined by the presence of technetium is demonstrated by the accumulation in bone of free HEDP, as well as its complexes with tin or rhenium.[20] Cobalt diphosphonate complexes have also been shown to bind Ca^{2+} ions[20] while the structure of $\{Tc(MDP)(OH)\}_n^{n-}$, shown in Figure 52, illustrates the capacity of MDP for bridging between metal centres.[590] The selective accumulation of HMDP and HEDP complexes of ^{99m}Tc at sites of new bone formation has been investigated by Francis and coworkers.[660] They proposed that these potentially tridentate calcium binding agents were preferentially bound to the (001) faces of the hydroxyapatite crystals in the bone. Since these crystals grow most rapidly along the *c*-axis, the (001) face containing this axis contributes more to the surface area of newly forming bone mineral than to that of old mineral. Thus a higher diphosphonate/calcium ratio would be obtained on newly forming as opposed to nongrowing bone tissue. The nature of the ^{99m}Tc complex bound to the bone remains uncertain, although the dissolution in EDTA of bone treated with ^{99m}Tc-MDP afforded a ^{99m}Tc product which could not be distinguished from ^{99m}Tc-MDP.[661]

The proportion of a ^{99m}Tc bone agent which is taken up by bone after intravenous injection will be affected by its binding to proteins in the blood serum.[551,553] The proportions of the plasma ^{99m}Tc which were protein bound two hours after administration were found[662] to be 16, 31, 54 and 85% with HEDP, MDP, PYP and tripolyphosphate respectively. In addition, the proportion of the administered dose of ^{99m}Tc which was taken up in bone was found to increase linearly with the fraction of ^{99m}Tc in the plasma which was not protein bound. Cox has reported a linear decrease in bone uptake with molecular weight for this series of bone agents,[663] an observation which appears to reflect differences in their plasma protein binding behaviour. Thus the blood serum proteins may compete with bone for the ^{99m}Tc complexes and reduce the bone labelling efficiency of the radiopharmaceutical. The ^{99m}Tc-diphosphonate formulations showed better performance in this respect than ^{99m}Tc-PYP or ^{99m}Tc-tripolyphosphate.

65.3.2.2 Kidney

Imaging agents for both kidney structure and kidney function studies are dominated by ^{99m}Tc formulations and near-ideal kidney agents are now available.[664] These renal agents may be divided into three types: those that are filtered, those that are secreted and those that exhibit mixed behaviour. The complexes formed between ^{99m}Tc and EDTA or DTPA are cleared from the blood by glomerular filtration and this has led to the use of ^{99m}Tc-DTPA as an agent for investigating kidney function.[553] Binding to blood serum protein may affect the filtration rate of ^{99m}Tc-DTPA so that allowance may need to be made for such effects when measuring renal function by this method.[665] However, alternative agents such as ^{51}Cr-EDTA or ^{169}Yb-DTPA do not appear to offer any advantages over ^{99m}Tc-DTPA in this application.[666] Some examples of renal images obtained using ^{99m}Tc-DTPA are presented in Figure 54.

At present, hippuric acid, $PhC(O)NHCH_2CO_2H$, labelled in the *ortho* position with ^{131}I, is the principal agent used for evaluating renal tubular secretory function, but the nuclear properties of ^{131}I or ^{123}I are far from ideal for this purpose.[665,667] This has stimulated the search for a ^{99m}Tc

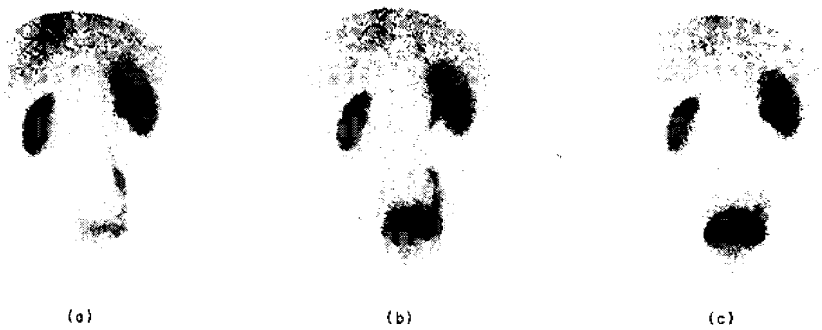
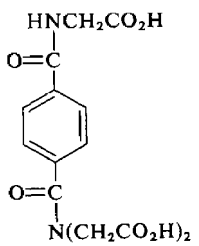
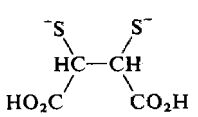


Figure 54 Renal images obtained using ^{99m}Tc-DTPA showing a normal right kidney and impaired function of the left kidney. The ^{99m}Tc activity can be seen to accumulate in the bladder at the bottom centre with increasing elapsed time from (a) to (c). (Courtesy of the Nuclear Medicine Department, Queen Elizabeth Hospital, Birmingham, UK)

agent suitable for studying renal secretion and measuring effective renal plasma flow. Two types of compound appear promising for this application.[667] The first includes complexes of ema, also known as DADS, and related species.[585,616,668,669] Rapid renal secretion was observed for ^{99m}Tc-DADS (**24**)[668] and its isomers in which one or both amide carboxyl groups were relocated in the central chelate ring.[616] A series of related compounds containing chelate rings of varying size has also been investigated using the ligands $\{X(NHC(=O)(CH_2)_nS^-)_2\}$, in which $n = 1$ and $X = (CH_2)_2$, $(CH_2)_3$ or o-C_6H_4, or $n = 2$ and $X = (CH_2)_2$ or $(CH_2)_3$. The ^{99m}Tc-DADS complex containing three five-membered chelate rings was found to be most readily formed, stable and rapidly excreted.[669] Unfortunately, biliary excretion of ^{99m}Tc-DADS also occurs and some depression of renal function has been found with this agent. In another study,[670] 27 analogues of DADS were evaluated and agents which gave satisfactory renal images with ^{99m}Tc were identified. However, these could only mimic the distribution behaviour of ^{131}I-hippuran (hippuran being p-$NH_2C_6H_4C(O)NHCH_2CO_2H$) in rabbits and not in other species, including man. This observation may have a bearing on a recent evaluation of a second type of kidney agent (**38**), which was used to complex ^{99m}Tc at pH 5–8 and gave good renal scans in rabbits.[671] The agent was readily excreted but renal clearance was lower than for ^{131}I-hippurate because of protein binding. Thus, although promising ^{99m}Tc agents are now available the ideal ^{99m}Tc replacement for ^{131}I-labelled hippurate remains to be identified.



(**38**)



(**39**)

Renal imaging agents which exhibit mixed behaviour may be useful in the study of kidney morphology. Examples of such agents include ^{99m}Tc-gluconate, ^{99m}Tc-glucoheptonate and, most prominently, ^{99m}Tc-DMSA, where DMSA is dimercaptosuccinic acid (**39**). The kidney uptake of a variety of Tc^{V} and Tc^{IV} carboxylic acid complexes has been studied and the retention of Tc^{V} species found to be higher than Tc^{IV} for citrate, tartrate, malate and hydroxyisobutanoate complexes.[672] The use of Sn^{II} to reduce $^{99m}TcO_4^-$ in the preparation of kidney agents has been found to increase ^{99m}Tc retention,[553,673] and the kidney uptake of ^{99m}Tc-DMSA was found to be affected by the conditions of $^{99m}TcO_4^-$ reduction. An investigation[674] of this phenomenon using ^{117m}Sn, ^{14}C and ^{99m}Tc labelling studies revealed that at an Sn-DMSA:Tc ratio in excess of 10^4, one ^{99m}Tc species was formed, but at lower ratios, four components were present. Two Sn-DMSA compounds were also identified using reversed-phase HPLC and ion exchange methods. A rather surprising structure was proposed for the ^{99m}Tc complex which exhibited renal uptake. This involved two tridentate DMSA ligands each bound to technetium through one carboxylate and two thiolate groups to give a six-coordinate complex. Based on known ^{99}Tc chemistry a structure

involving only thiolate binding to TcO^{3+} as found in (**23**), or involving the additional binding of one carboxylate group *trans* to the oxo ligand as found in (**27**), might have been expected. Renal uptake was found to occur in the microsomes of the proximal tubular cells and it was proposed that the uptake mechanism involved binding to protein by the displacement of one DMSA ligand, which was excreted, from $^{99m}Tc(DMSA)_2$. An improved protocol for preparing the ^{99m}Tc–DMSA agent was described to overcome the variability in performance observed previously. Agents incorporating ^{97}Ru, which has a 2.9 day half-life and emits a 216 keV γ-ray, have also been proposed as kidney agents. These included a complex with 2,3-dimercaptopropanesulfonic acid and DMSA which proved suitable for delayed renal scintigraphy in dogs.[675] However, it is unlikely that these will replace ^{99m}Tc–DMSA for general clinical use.

65.3.2.3 Hepatobiliary system

As was the case for kidney imaging, ^{99m}Tc formulations now dominate the hepatobiliary agents in current clinical use. Historically, ^{131}I-labelled rose bengal was used for liver function studies but in the late 1970s this was superseded by the ^{99m}Tc-iminodiacetate agents. These employed substituted derivatives of iminodiacetic acid (IDA) such as (**21a**), (**21b**) or (**21c**) as the complexing agent. The ability of ^{99m}Tc complexes of IDA derivatives to undergo rapid hepatobiliary excretion was discovered[676] accidently by Loberg and coworkers, who were using (**21a**) as an analogue of the antiarrhythmic drug lidocaine (**21b** in which the CO_2^- moieties are replaced by methyl) which accumulates in the heart. The free ligand was found to be rapidly excreted through the kidneys while the ^{99m}Tc complex was excreted through the liver and bile duct.

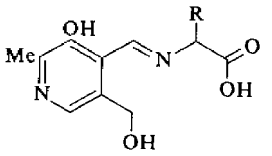
The hepatobiliary agents are removed from the blood by hepatocytes in the liver through an active transport mechanism.[677] They are cleared from the plasma as anions by the same general mechanism as bilirubin so that high bilirubin levels can competitively inhibit the transport of ^{99m}Tc–IDA agents through the liver.[553]

Several studies of the relationship between structure and biodistribution have been carried out on the ^{99m}Tc–HIDA derivatives and related compounds.[553,678] The more hydrophilic agents, such as ^{99m}Tc-methyliminodiacetic acid, are excreted primarily through the kidneys.[679] However, as the lipophilicity of the agent increases, hepatobiliary excretion becomes more important and is the dominant route for ligands such as (**21a**). Furthermore, increasing alkyl substitution of the aromatic ring in (**21a**), other than at the *ortho* positions, increases the ratio of hepatobiliary to renal excretion.[20,553] Burns and coworkers have established a linear correlation between the logarithm of the mass-to-charge ratio of a series of *para*-substituted HIDA derivatives and the proportion of hepatobiliary excretion.[635] Substitution of the *ortho* positions in ^{99m}Tc–HIDA appeared to promote lability in at least one technetium coordination site and was also associated with an increase in protein binding, which had been negligible for ^{99m}Tc–HIDA itself.[20,652,680]

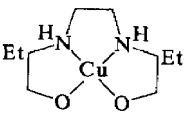
Substitution of the *ortho* positions also promoted urinary as opposed to biliary excretion of ^{99m}Tc-labelled HIDA derivatives.[68] The radiochemical purity of the ^{99m}Tc–HIDA formulations was found to be dependent upon the preparative conditions used. At least two components were identified[582] in formulations with (**21c**) and the pH of the preparative medium and the pK_a of the complexing agent appear to be important factors affecting radiochemical purity.[682]

The Schiff bases derived from pyridoxal and amino acids having the general structure (**40**) have also been investigated as potential liver imaging agents for use with ^{99m}Tc.[553,683–685] When complexed with ^{99m}Tc the ligand derived from methyltryptophan (**40**; $R = CH_2C_8NH_5Me$) exhibited rapid clearance from the blood and was less sensitive to competition from serum bilirubin than the ^{99m}Tc complex of (**21c**). A study of the structure–distribution relationships in the phenylalanine derivatives (**40**; $R = CH_2Ph$ and aryl substituted derivatives) showed[685] that increasing total lipophilicity was associated with decreased urinary excretions, as found for IDA derivatives. Lipophilic substituents in the *para* position of the phenylalanine aryl group gave rise to slower hepatobiliary transit, while substituents in the *ortho* position gave rise to accelerated transit. Both sets of substituents depressed urinary excretion but those in the *ortho* position appeared to dominate the behaviour of the ^{99m}Tc complex.[685] Other ligands which have been evaluated for use with ^{99m}Tc include derivatives of ethylenediamine-*N*,*N*-diacetic acid[686] and derivatives of IDA which contain naphthyl substituents.[687] It remains to be seen whether such agents can offer advantages over the existing HIDA derivatives in clinical use.

Studies of liver structure may be carried out using colloidal dispersions labelled with ^{99m}Tc.[551] The ^{99m}Tc–sulfur colloid provides one such example and is usually described as $^{99m}Tc_2S_7$, although its chemical composition remains uncertain. An improved method for the preparation of this



(40)



(41)

material has been described[688] recently based on the prior binding of Sn^{II} to sulfide generated from thioacetamide, followed by the addition of $^{99m}TcO_4^-$. The product formed behaved as a combination of two components with biological half lives of 3 and 67 minutes.

Nuclides other than ^{99m}Tc which have been evaluated for use in liver studies include ^{64}Cu and ^{61}Cu as complexes of the tubercularstatic agent Myambutol (**41**). These were proposed for the evaluation of liver function.[689] The use of ^{67}Ga citrate in diagnosing the Budd Chiari syndrome, occlusion of a vein in the liver, has also been described but ^{99m}Tc formulations are also suitable for this purpose. Perhaps the most interesting alternative to ^{99m}Tc is provided by ^{97}Ru, which has a longer half-life and is thus suited for studies requiring delayed scintigraphy. A preparation of ^{103}Ru chloride containing Ru^{III} and Ru^{IV} was found to exhibit similar biological behaviour to that of ^{99m}Tc with two derivatives of HIDA.[691] This suggests that ^{97}Ru agents may be developed for use in delayed scintigraphic studies of the liver, where ^{99m}Tc might be unsuitable.

65.3.2.4 Heart and Brain

A variety of nuclides, including ^{99m}Tc, ^{201}Tl, ^{43}K, ^{129}Cs and ^{81}Rb, has been used as agents for heart imaging.[692] Among these, ^{201}Tl has predominated in the study of infarcted and ischemic areas of the heart.[514,693] Intravenously injected $^{201}Tl^{I}Cl$ is rapidly removed from the blood and accumulates in myocardial tissue. The accumulation mechanism remains uncertain and one view is that uptake is mediated by Na/K ATP-ase and depends upon blood flow according to a capilliary clearance model.[514,694] However, other workers have suggested[584,694] that Na/K ATP-ase is not involved. Furthermore, a cationic absorption route similar to that associated with potassium uptake would not be in accord with electrophoretic studies, which have shown that the ^{201}Tl species present in blood serum are anionic in nature.[693] The anionic species was formulated as $TlCl_4^-$ in this study, but it is unlikely that Tl^{III} would be stable under physiological conditions and Tl^{I} complexes such as $TlCl_2^-$ or $TlCl_3^{2-}$ would seem more realistic candidates. The bone agent ^{99m}Tc-MDP and related complexes have also been found to accumulate in damaged myocardial tissue.[696] This phenomenon does not appear to be directly related to the Ca^{2+} levels found in regions of cellular necrosis and both myocardial and bone tumor uptake of ^{99m}Tc-phosphonate agents may involve an active cellular uptake mechanism.[697,698] Clinical trials have indicated that ^{99m}Tc-imidodiphosphonate is superior to either MDP or pyrophosphate formulations in myocardial imaging applications.[696]

Lipophilic substances such as fatty acids have also been found to accumulate in the myocardium[699] and this has prompted a search for ^{99m}Tc agents which might replace ^{201}Tl in heart imaging applications. However, the binding of ^{99m}Tc to 2-mercaptohexadecanoic acid and related substances[700] or to $HO_2C(CH_2)_nN(CH_2PO_3H_2)_2$ ($n = 1, 3, 5, 7, 11, 15, 17$)[701] did not lead to agents which exhibited myocardial accumulation. The binding of the ^{99m}Tc thus altered the biodistribution of the fatty acid ligands. More promising results have been obtained with the cationic Tc^{III} complexes $[Tc(L{-}L)Cl_2]^+$, where L—L = diars, or dmpe.[20] As with other agents, the more lipophilic systems were excreted through the hepatobiliary system and the more hydrophilic through the kidneys. The least lipophilic complex, $[^{99m}Tc(dmpe)_2Cl_2]^+$, was found to exhibit the lowest liver uptake and gave the highest myocardial uptake.[20,583] The diars complex gave lower myocardial accumulation,[614] and both complexes showed lower uptake than ^{201}Tl; the relative proportions accumulated 1 minute after injection were 9.4%, 11.7% and 25% for ^{99m}Tc-diars, ^{99m}Tc-dmpe and $^{201}Tl^+$ respectively.[613] A formulation for the preparation of the ^{99m}Tc-dmpe agent has been patented[702] and involves the reaction of $^{99m}TcO_4^-$ with $[dmpeH_2]^{2+}(HSO_4^-)_2$ at 135 °C over 15 minutes in the presence of propane-1,2-diol at low pH. The reaction of TcO_4^- with dmpe in HCl/EtOH at 90–95 °C was found to give more than one cationic complex but only one ^{99m}Tc species showed myocardial uptake.[703] Cationic Tc^{I} complexes also show myocardial uptake and in particular the isocyanide complexes $[Tc(RNC)_6]^+$ (R = Me, Et, Pr^n, Pr^i, Bu^n or Bu^t) have been investigated as heart agents.[607,704] The complex $[^{99m}Tc(Bu^tNC)_6]^+$ gave the best results but its clinical value as a replacement for ^{201}Tl in myocardial imaging applications has yet to be

established. A formulation for the preparation of this agent from $[^{99m}Tc(tu)_6]^{3+}$, which may itself be prepared directly from $^{99m}TcO_4^-$, has been patented.[705] These agents may also be utilized for blood cell labelling, which is considered in more detail in Section 65.3.2.6. The complex $[^{99m}Tc(Bu^iNC)_6]^+$ was found to be the most effective in this role.[704] Among other applications,[505] labelled blood may be used to study heart function.[505] Agents such as ^{99m}Tc-DTPA, which are cleared from the blood quite rapidly, are less well suited for delayed studies than ^{99m}Tc-labelled red blood cells (RBC) or human serum albumin (HSA), which are not excreted.

In the case of brain imaging, a special problem is encountered by the radiopharmacist in that the blood/brain barrier (BBB) prevents many substances from entering the brain. As was found for myocardial agents, lipophilicity appears to be an important property of compounds which can cross the BBB. Thus complexes of $RN(CH_2CH_2SH)_2$ (R = H, Me, Et, Bu or hexyl) with ^{99m}Tc showed some ability to cross the BBB,[706] while complexes with *N*-alkylated cyclam derivatives, thought to contain the hydrophilic TcO_2^+ core, did not.[602] One means of assessing the lipophilicity of a compound is to measure its octanol:saline partition coefficient and it has been proposed that values of greater than 0.5:1 are indicative of substances which may undergo passive membrane transport.[707] However, lipophilicity alone is insufficient to define an effective brain imaging agent. The ^{99m}Tc complexes of (**35**) were taken up by the brain but their retention times were too short for imaging applications.[648,649] One way of increasing brain retention times might be to exploit the slightly lower pH prevailing inside the brain. Thus agents carrying substituents which could protonate after entering the brain, and thereby reduce their membrane permeability, might become trapped and show longer-term retention. This approach has been applied[708] in the case of radio-iodine labelled *N,N,N'*-trimethyl-*N'*-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine, for example, and may find application in ^{99m}Tc agents of the future. A further problem encountered in the use of lipophilic agents is their tendency to bind to serum proteins. This is exemplified by the ^{68}Ga complexes of some *N*-alkylated derivatives of LICAM (**17**), which were investigated as potential brain imaging agents.[709] These were strongly bound by high molecular weight serum proteins and rendered unsuitable for brain studies.

The principal brain imaging agents in use at present are $^{99m}TcO_4^-$, ^{99m}Tc-DTPA and ^{99m}Tc-glucoheptonate.[505,551] None of these agents actually permeates through the BBB and their accumulation in the brain results from the disruption of the BBB by tumours or lesions.[710] Some examples of brain images obtained using ^{99m}Tc-glucoheptonate are presented in Figure 55 and demonstrate

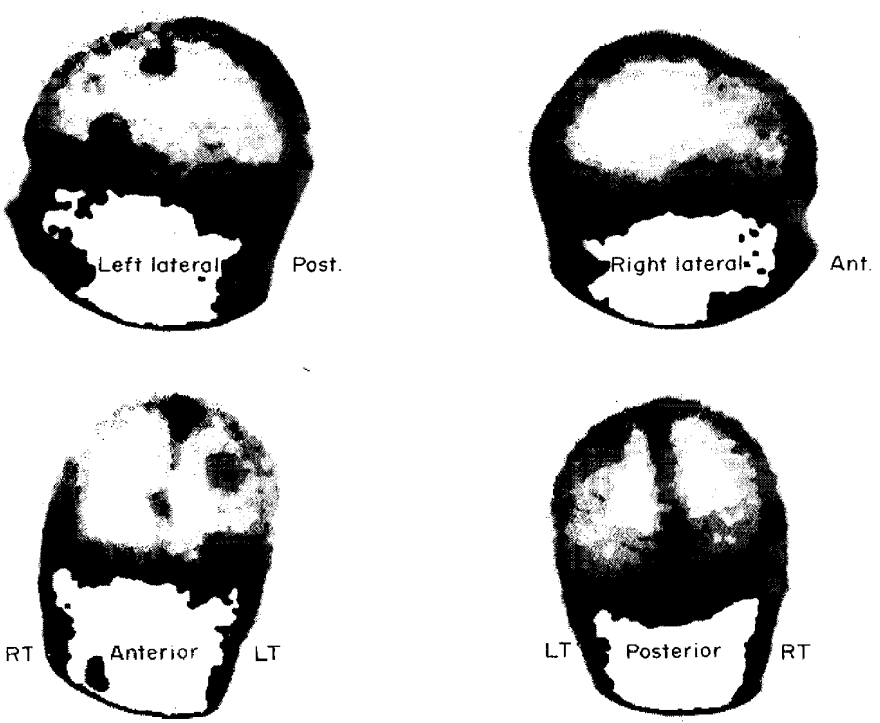


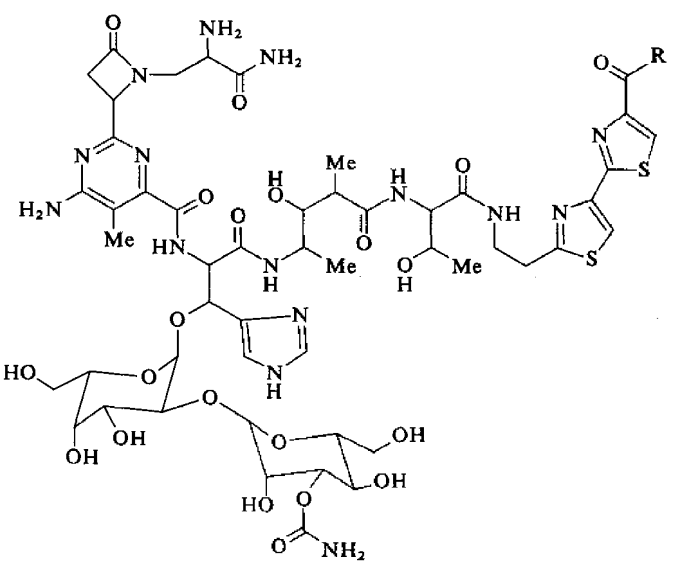
Figure 55 Brain images obtained using ^{99m}Tc-glucoheptonate showing the location of secondary tumors which disrupt the blood brain barrier. (Courtesy of the Nuclear Medicine Department, Queen Elizabeth Hospital, Birmingham, UK)

the utility of ^{99m}Tc agents for diagnosing diseases which lead to breakdown of the BBB. A normal brain scan would show essentially no ^{99m}Tc uptake. However, the application of diagnostic imaging to diseases of the brain which do not involve disruption of the BBB requires the development of an agent which is lipophilic, retained in the brain, not rapidly excreted by the hepatobiliary system and not extensively bound by serum protein.

65.3.2.5 Tumors and abscesses

Although a variety of radiopharmaceuticals have been proposed for tumor imaging, most are suitable only for a particular type of tumor and are not of general utility.[505] This has somewhat limited the applications of imaging techniques in this area of diagnostic medicine. The nuclide of greatest general use in tumor studies is ^{67}Ga, which is normally administered as its citrate complex. A review of tumor scanning using ^{67}Ga concluded[711] that this was not a good general screening agent because of the high proportion of false negative results obtained. However, when used in conjunction with other data the technique was valuable and produced few false-positive indications. The mechanism of accumulation of ^{67}Ga at tumor sites is not well understood. After injection the ^{67}Ga is taken up by transferrin (Tf) and equilibrium constants of $10^{23.7}$ and $10^{22.3}$ mol^{-1} have been reported for the uptake of the first and second Ga^{3+} ions respectively.[712] The binding of Ga^{3+} to Tf correlated well with the capacity of the serum to bind free iron and was enhanced by bicarbonate ions.[713] In fact, Fe^{3+} and Ga^{3+} have been reported to follow kinetically equivalent transport pathways.[714] The transfer of ^{67}Ga into tumor cells was found to be greater from Tf than from the citrate complex and the binding of ^{67}Ga labelled Tf to cell surface receptor sites was proposed to account for this.[715] Studies carried out *in vitro* showed that ^{67}Ga could be transferred from Tf to ferritin in a process stimulated by small molecules such as adenosine triphosphate.[716,717] However, on the basis of *in vivo* studies it was claimed that ferritin was not the site of ^{67}Ga localization.[718] Since lactoferrin (Lf) can compete with Tf for Ga^{3+} it has been proposed that this serum protein may serve to localize ^{67}Ga transferred from Tf.[719] Levels of Lf may be elevated in the region of tumors as part of an inflammatory response so that this protein is a promising candidate for the role of a ^{67}Ga localizing agent.[515] However, the potential role of ferritin in localizing ^{67}Ga at tumor sites cannot be discounted.[515] The accumulation of ^{67}Ga in abscesses or inflammatory lesions may also involve binding to Lf as well as to bacterial siderophores and to leukocytes. Since the ^{67}Ga is transported to the lesion by serum Tf, a good blood supply is necessary for useful images to be obtained. However, the ^{67}Ga activity remaining in the blood may mask the image of the target site. This problem may be countered by injecting iron, to saturate the binding sites in normal tissue and blood, or Ga^{3+} sequestering agents to promote urinary excretion of the residual ^{67}Ga in the blood.[721,722]

Another agent which has found application in tumor imaging is ^{111}In-bleomycin.[505] The bleomycins are naturally occurring water-soluble copper-containing glycopeptide antibiotics having the generic structure (**42**), in which R may be a variety of substituent as shown in Table 23.[723]

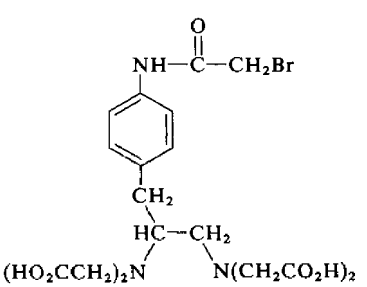


(**42**)

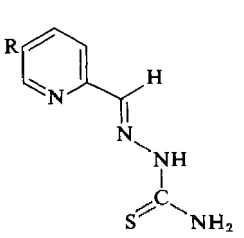
Table 23 The Nature of the Variable Region in Bleomycin[723]

Bleomycin	*R group in* (42)
A_1	$-NH(CH_2)_3S(=O)Me$
A_2	$-NH(CH_2)_3SMe_2^+$
Demethyl A_2	$-NH(CH_2)_3SMe$
A_{2a}	$-NH(CH_2)_4NH_2$
A_{2b}	$-NH(CH_2)_3NH_2$
A_{2c}	$-NH(CH_2)_2-C(=CH-NH-CH=N)-$
A_5	$-NH(CH_2)_3NH(CH_2)_4NH_2$
A_6	$-NH(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$
B_1	$-NH$
B_2	$-NH(CH_2)_4NHC(=NH)NH_2$
B_4	$-NH(CH_2)_4NHC(=NH)NH(CH_2)_4NHC(=NH)NH_2$
Bleomycinic acid	$-OH$

These compounds are used in tumor therapy and their mode of action appears to involve DNA cleavage in an iron mediated redox process.[519] The bleomycin molecule can bind to DNA through the bithiazole moiety and can also bind iron in a manner which involves the aminopyrimidine and imidazole moieties.[519] The combination of tumor localizing and metal binding properties in bleomycin suggested that it would be a suitable agent for localizing radionuclides at tumor sites. A variety of metallic radionuclides, including ^{57}Co, ^{59}Fe, ^{62}Zn, ^{64}Cu, ^{67}Ga, ^{99m}Tc and ^{111}In, were therefore evaluated for use with bleomycin.[723,724] The ^{57}Co complex appeared to be the most stable and showed the best tumor/blood activity ratios, while labelling with ^{99m}Tc did not give a stable chelate. The binding of ^{67}Ga to bleomycin appeared to involve a 1:1 stoichiometry but the complex was of limited stability and had a lifetime of the order of 15 s at 343 K.[725] The ^{111}In-bleomycin complex has found greater medical utility in spite of its similarly limited *in vivo* stability. As with Ga^{3+}, In^{3+} is bound by serum Tf and the equilibrium constants for the formation of $Tf(In^{3+})$ and $Tf(In^{3+})_2$ have been reported at $10^{30.5}$ and $10^{25.5}$ respectively.[712] Thus after ^{111}In-bleomycin administration, serum Tf competes with bleomycin for the ^{111}In and can act as an alternative transporting agent. However, the ^{111}In does not subsequently accumulate in iron-utilizing organs but instead appears to be localized by binding to mucopolysaccharides.[726] Such binding sites have also been proposed to account for the localization of ^{67}Ga in tumor tissue.[727] In practice it seems that ^{111}In-bleomycin offers little advantage over ^{67}Ga-citrate as a tumor imaging agent and in some cases the ^{67}Ga agent performs better.[724,728] In an attempt to improve the radionuclide binding properties of bleomycin, Meares and coworkers have investigated the incorporation of an EDTA substituent into the molecule to provide a second metal-ion binding site.[19,729] The original metal binding site in bleomycin-A_2 was blocked by complexation to Co^{3+} and two isomers were obtained. The first of these was green and was converted over a period of days to a stable orange isomer. Although the green isomer exhibited superior tumor localization properties, for convenience the stable orange isomer was used in subsequent reactions. The transalkylation of the $-SMe_2^+$ group in this compound, using the reagent (**43**), afforded a Co^{III}-bleomycin derivative, BLEDTA, carrying an EDTA-containing substituent. BLEDTA labelled with ^{111}In showed higher tumor uptake in mice than ^{111}In-labelled phenyl-EDTA and was far more selective in distribution that ^{111}In-bleomycin-A_2.[729] Although the clinical value of this agent has yet to be fully assessed, the demonstration that a drug known to exhibit a particular biodistribution can be modified and labelled, without destroying its *in vivo* localization properties, represents an important landmark in radiopharmacy.



(43)



(44)

In some cases, drugs known to have tumor localizing properties may be labelled with metallic radionuclides under synthetically less demanding conditions. Certain thiosemicarbazone complexes of iron or copper, for example, inhibit ribonucleoside diphosphate reductase, which is more active in tumor cells than in normal tissue. Accordingly, the ^{59}Fe complexes of (**44**), in which R = H, NMe_2 or OH, have been investigated as agents for locating tumors.[730] Some selectivity for transplanted glioblastomas in rats was found using these agents. Another example is provided by ^{203}Hg-labelled estradiol, which has been evaluated for the location of mammary tumors. In rats, tumor/normal tissue activity ratios of between 5 and 14 were obtained with estradiol labelled in the 2- or 4-positions.[731] The labelling of relatively small molecules in this way may provide a route to new radiopharmaceuticals for diagnostic use. However, in cases where drug labelling does not involve the simple replacement of a stable isotope by a radioactive one, the effect of the labelling group on the *in vivo* behaviour of the molecule may be dramatic and examples such as ^{111}In–BLEDTA or ^{203}Hg–estradiol may prove to be the exception rather than the rule. In spite of this, the search for imaging agents based on molecules of known biodistribution would seem worthwhile. In particular, a general synthetic approach to the labelling of organ-selective drugs with ^{99m}Tc would represent an important innovation.

65.3.2.6 Labelled colloids, cells and proteins

Radiolabelled particulate or macromolecular species have a variety of applications in diagnostic nuclear medicine.[505,732] The colloid obtained by the reduction of $^{99m}TcO_4^-$ in the presence of sulfur and sulfide ions, for example, may be used for liver and spleen imaging, and in some cases bone marrow lymphatic system imaging. Human serum albumin (HSA) aggregated to a particulate form and labelled with ^{99m}Tc may be used for lung perfusion imaging,[733] while ^{198}Au colloid or ^{99m}Tc-labelled Sb_2S_3 particles have been used in lymphatic system studies.[734] Blood pool imaging, heart function evaluation and the study of red blood cell sequestration by the spleen are all possible using red blood cells labelled with ^{51}Cr, ^{99m}Tc or ^{111}In,[505,636,735] and leukocytes labelled with ^{111}In may be of use in the detection of abscesses or inflammatory lesions. Proteins such as fibrinogen, HSA or antibiotics may also be labelled and, in particular, ^{99m}Tc-labelled HSA may be used to study cardiac output and blood volume.[505,736]

The preparation of labelled blood cells normally involves their removal from the patient, purification, treatment with the labelling agent and re-injection into the patient. For ^{111}In or ^{68}Ga such a process can be inefficient because of the binding of the In^{3+} or Ga^{3+} ions to serum proteins, especially to Tf. However, if these ions are first complexed by 8-hydroxyquinoline to produce lipophilic species, presumed to be the neutral tris complexes, efficient labelling of red blood cells, platelets or leukocytes is possible.[23,524,737] Recently it has been shown that 2-mercaptopyridine *N*-oxide may also be used to label platelets and leukocytes with ^{111}In. In the case of leukocytes, good accumulation in abscesses was found in dogs with lower liver uptake than for ^{111}In–oxine labelled leukocytes.[738] The efficiency of platelet labelling using ^{99m}Tc–oxine was found to be lower than for ^{111}In–oxine,[637] but could be improved using a procedure involving the electrolytic generation of controlled amounts of Sn^{II} rather than excess $SnCl_2$ as the reductant.[638] The reasons for this have been elucidated in a mechanistic study of red blood cell labelling by ^{99m}Tc.[739] In the citrate medium used to suspend the blood cells, Sn^{2+} was complexed by citrate and entered the cell. The $^{99m}TcO_4^-$ was able to diffuse in and out of the cell, but where intracellular Sn^{II} was present it was reduced and became bound predominantly by the β-globin chain of hemoglobin. The Sn^{IV} and reduced ^{99m}Tc were then trapped within the cell. Where extracellular Sn^{II} was present the $^{99m}TcO_4^-$ was prematurely reduced and prevented from entering the cell. Higher labelling efficiencies could thus be obtained by treating the cell suspension with excess Sn^{II}, then oxidizing the extracellular tin to Sn^{IV} after the cells had taken up some Sn^{II}. EDTA was also added to sequester the Sn^{IV} and subsequent treatment of the blood cells with $^{99m}TcO_4^-$ gave a labelling efficiency in excess of 95%.[739]

Another ligand which has been investigated for blood cell labelling applications is penicillamine. This formed a neutral lipophilic complex with ^{99m}Tc which was presumed to contain a TcO^{3+} core.[592] However, the labelling efficiency achieved with this agent was only 83%.[740] Extensive use has been made of ^{51}Cr in the labelling of red blood cells.[505] This is normally effected by treating a cell suspension with $^{51}CrO_4^{2-}$ followed by reduction of the residual extracellular ^{51}Cr to Cr^{III}, which does not enter the cells. The labelled cells may be used for measuring the mass and survival of the *in vivo* blood cell pool. The function of the spleen may also be studied if the labelled cells are denatured at 50 °C for 20 min before administration. The labelling of lymphocytes with ^{99m}Tc,

^{111}In or ^{51}Cr has been assessed in rats and, of the agents studied, ^{111}In–oxine was found to be the best.[741] The nuclear properties of ^{51}Cr, as well as its *in vivo* behaviour, were unsuitable for imaging purposes, while the ^{99m}Tc label was found to be readily lost.

Human plasma proteins such as serum albumin, fibrinogen or immune γ-globulin may be labelled using $^{99m}TcO_4^-$ and a reducing agent, usually Sn^{II}.[505,551,742,743] The preparation may be freed of unbound $^{99m}TcO_4^-$ by ion exchange procedures and the ^{99m}Tc label is sufficiently stable *in vivo* for imaging purposes, although its mode of binding to the protein remains uncertain. Fibrinogen[744] or plasmin[745] labelled in this way have attracted attention as agents for the diagnosis of deep vein thrombosis. The labelling procedure does not appear to impair drastically the biological properties of these proteins and ^{99m}Tc-fibrinogen offers a promising alternative to ^{125}I-labelled fibrinogen for thrombosis investigation. The labelling of proteins with ^{67}Ga or ^{111}In represents a more difficult problem because of the more labile chemistry exhibited by Ga^{3+} and In^{3+}, combined with the affinity of Tf for these ions. In order to overcome these problems, attempts have been made to attach polydentate chelating ligands to proteins to provide more powerful metal ion sequestering sites. Thus HSA has been linked to the naturally occurring Fe^{3+} sequestering agent, desferrioxamine, using glutaraldehyde[746] or succinic anhydride[747] as coupling agents. The modified protein could then bind $^{67}Ga^{3+}$ sufficiently strongly for the label to be retained *in vivo*. Fibrinogen has also been labelled with ^{67}Ga after treatment with DTPA anhydride to attach DTPA binding sites to the protein.[748] The reaction of the diazo compound (**19**) with proteins provides a means of attaching EDTA substituents, and HSA modified in this way was found to retain a ^{111}In label for two weeks when incubated in serum.[547] Such protein labelling procedures are now well established experimentally and are being developed for clinical use.

Perhaps the most exciting potential application of such protein modification techniques is in the radiolabelling of antibodies. The advent of monoclonal antibody technology has provided the radiopharmacist with a potentially powerful group of agents for transporting radionuclides to specific sites in the body. However, despite their great promise, monoclonal antibodies present many difficult technical problems which will need to be solved before they can find widespread use in diagnostic imaging or radiotherapy applications.[749] Many of these problems are of a biochemical or immunological nature and cannot be addressed by the coordination chemist. However, the development of reagents which can effect the irreversible binding of metallic radionuclides to antibodies in a manner which does not affect antibody specificity offers considerable scope for chemical innovations. At present the most widespread technique for antibody labelling appears to involve reaction with DTPA anhydride and the original labelling method[520] has now been optimized.[750] Antibodies modified in this way have been labelled with ^{111m}In, ^{113}In or ^{99m}Tc. The labelling procedure may deactivate the antibody or reduce its specificity. In one example, a near statistical distribution of a ^{111}In label between free DTPA, active modified antibody and non-active modified antibody was found.[751] An antibody for a human melanoma associated antigen has also been modified using DTPA anhydride then labelled with ^{111}In.[752] The labelled antibody again showed some loss of activity and poorer localization properties than its precursor. Another problem which arose was the high hepatic and renal uptake of the label. The labelling efficiency of an anti-HSA antibody was found to be below 25% using the DTPA anhydride/^{111}In system, but the reactivity towards $^{111}In^{3+}$ of antibodies carrying more than one DTPA substituent was similar to that of free DTPA.[753] In contrast, labelling efficiencies of 50–75% have been reported for the ^{111}In labelling of immunoglobulin G antibodies to a carcinoembryonic antigen (anti-CEA). A clinical study using ^{111}In–anti-CEA indicated that this agent could perform better than ^{131}In-labelled anti-CEA in identifying tumor sites.[754] An alternative approach has been described for binding ^{113m}In to immunoglobulin-G (IgG) which exploits the affinity of Tf for In^{3+}. Using NTA as a carrier ligand, $^{113m}In^{3+}$ was bound to Tf in the presence of HCO_3^-. The labelled Tf was then coupled to IgG using glutaraldehyde.[755] The coupling of EDTA to monoclonal antibodies has also been described.[756] Derivatives of EDTA containing *p*-bromoacetamidobenzyl or *p*-isothiocyanatobenzyl substituents on the ethane moiety were reacted with antibody preparations and ^{57}Co-labelling used to assay the extent of modification. In this way, conditions for attaching between one and two EDTA substituents per antibody could be defined.

The labelling of antibodies with ^{99m}Tc appears to be rather more problematic than that with indium isotopes. The variety of technetium oxidation states which may exist *in vivo*, and the need to reduce $^{99m}TcO_4^-$, complicate procedures for labelling with this nuclide. Nonspecific protein sites, as well as the chelating substituents artificially attached to the protein, can bind ^{99m}Tc, and in DTPA-modified antibodies, nonspecific binding cannot be eliminated.[757] Thus even though the artificially introduced chelating sites may irreversibly bind ^{99m}Tc, the label can be lost from the non-specific binding sites after labelling and give rise to a radiation background whose distribution

differs from that of the antibody. Between two and five DTPA substituents per antibody appear to be necessary for effective ^{99m}Tc labelling, but the choice of a reducing agent for $^{99m}TcO_4^-$ appears to be important. Typically, Sn^{II} would be used for this purpose and appears effective in the case of DTPA modified antibodies.[758] However, the use of dithionite was reported to result in the labelling of nonspecific sites on the protein rather than at the attached DTPA sites.[759] Other studies have indicated[760] that the presence of bulky substituents on EDTA can reduce the rate of complexation of ^{99m}Tc. Consequently, attachment of DTPA or EDTA to an antibody may involve a kinetic penalty in the ^{99m}Tc complexation step which could enhance the effects of competing binding sites. Thus, although ^{99m}Tc labelling of antibodies is possible, a number of problems remain to be adequately defined and then solved. However, the benefits to diagnostic medicine of a generally applicable and effective ^{99m}Tc labelling procedure for monoclonal antibodies would be great, and there need be no doubt that work on this aspect of radiopharmacy will expand.

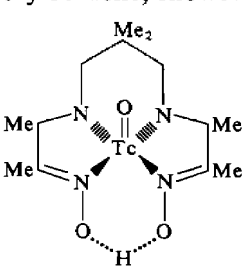
The attachment of radionuclides to site specific antibodies also offers the promise of 'nuclear magic bullets'[762] for use in radiotherapy. A DTPA modified IgG antibody, for example, has been labelled with the β-emitter ^{90}Y to give a potential tumor therapy agent. The behaviour of the Y^{3+} appeared similar to that of In^{3+} and the dissociation rate of the ^{90}Y label in serum at 37 °C was some 8–9% per day. However, although such experiments hint at promise for the future, formidable problems remain to be solved. In therapeutic applications it is especially important that any nonlocalized label is rapidly eliminated from the body, otherwise unacceptable radiation doses to nontarget tissues might result. If highly efficient and irreversible antibody labelling were achieved, without loss in antibody activity or specificity, then rapid localization of the radionuclide at the target site might be possible. Unfortunately, that would not be the only requirement since breakdown of the localized antibody would eventually occur, leading to a redistribution of the label. It could thus be necessary for any labelled antibody breakdown products to be rapidly excreted if high radiation doses to organs such as the liver and kidneys were to be avoided.

Radiopharmacy has come a long way since the work of Hevesey and of Blumgart and Weiss but developments in instrumentation, chemistry and immunology continue to offer new horizons and new challenges for the future.

65.4 RECENT DEVELOPMENTS

Several chemical developments in technetium radiopharmaceuticals were described at the Second International Symposium on Technetium Chemistry in Padua during September 1985. This included a report by Deutsch of the preparation of $[Tc(PMe_3)_2(acac_2en)]^+$ from $[TcO(acac_2en)]^+$ by reaction with PMe_3. The new complex was found to be more stable towards *in vivo* reduction to Tc^{II} than $[Tc(dmpe)_2Cl_2]^+$ and showed a heart uptake similar to that observed for $[Tc(CNBu^t)_6]^+$. Davison also described improvements to these hexakis(isocyanide) heart agents. The new complex $[Tc\{CNC(Me)_2CO_2Et\}_6]^+$ exhibited a similar heart uptake to its $CNBu^t$ analogue but with an improved heart/liver uptake ratio, allowing superior heart images to be obtained.

A new agent with potential for heart imaging was also described by Mallinckrodt. This was formed by the reduction of $^{99m}TcO_4^-$ with $Al/AlCl_3$ in the presence of arenes to give $[^{99m}Tc(arene)_2]^+$. Although the benzene complex showed no heart uptake, more lipophilic complexes, such as that of 1,2,3,5-tetramethylbenzene, showed significant myocardial uptake.



(45)

Finally, the highlight of the conference was the report by Amersham International of the launch of a brain scanning agent based on a tetradentate dioxime ligand. Preliminary studies indicate[763] that the active complex might have the structure (45) in which the amine nitrogens are deprotonated to give a neutral, lipophilic complex containing the $\{^{99m}TcO\}^{3+}$ core. In the development of this new agent, coordination chemistry has provided yet another tool for clinical use.

65.5 REFERENCES

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66

Other Uses of Coordination Compounds

ALWYN SPENCER
Ciba-Geigy AG, Basel, Switzerland

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66.1 TITANIUM, ZIRCONIUM AND HAFNIUM

66.1.1 Titanium

Absorption of hydrogen by titanium metal above 400 °C gives a solid whose stoichiometry approaches TiH_2, but a true dihydride does not appear to exist. This hydride has been used for the formation of glass-to-metal and ceramic-to-metal seals.[1] Thermal desorption above 600 °C provides a source of very pure hydrogen.[2]

Barium titanate, $BaTiO_3$, finds application as a ceramic material,[3] and is primarily of interest as a result of its electrical properties (see Chapter 60).

K_2TiF_6, in addition to applications in metallurgy, is used in the preparation of dental fillings.[3] $[Ti(H_2O)_6]Cl_3$ is used as a bleaching agent in cases where chlorine is inapplicable.[4]

Many transition metal compounds show smoke-retarding properties in poly(vinyl chloride). $TiO(acac)_2$ is notable in this respect. In so far as TiO_2 has even better smoke-retarding properties, it is possible that the acetylacetonate is converted to this on combustion.[5]

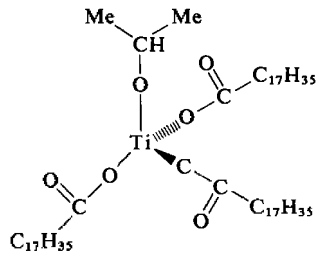
Titanium alkoxyesters and their derivatives are of considerable importance as a result of their ability to modify the properties of various kinds of plastics and coatings. The ease of formation and stability of the titanium–oxygen bond is the basis for these phenomena, which in the literature are summarized under the terms 'coupling agents' or 'crosslinking agents'. The applications include

the waterproofing of paper, textiles and masonry, silicone curing, treatment of glass surfaces, heat resistant paints, adhesive promotion, alkene polymerization and epoxy curing, and crosslinking in polyesters.

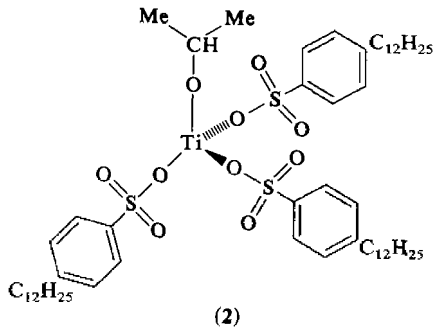
$Ti(OPr^i)[OP(O)(OC_8H_{17})_2]_3$, $Ti(OPr^i)[OS(O)_2C_6H_4C_{12}H_{25}]_3$ and $[Ti(OC_8H_{17})_4\{OP(OC_{12}H_{25})_2\}_2]^{2-}$ reduce the viscosity of araldite, polystyrene and poly(vinyl chloride) respectively, leading to improved dispersion properties. They also act as flame retardants and increase hydrophobicity.[7]

$Ti(OPr^i)[O_2C(Me)CH(CH_2)_{14}Me]_3$ reduces the melt viscosity of polyethylene and polypropylene and the resulting polymers show significantly improved elongation and impact strength.[8] $Ti(OPr^i)_2[O(CH_2)_2N(CH_2CH_2OH)_2]_2$ improves the physical and mechanical properties of alkyd resin coatings.[9] $Ti(OCH_2CO_2)[OP(O)(OH)OP(O)(OCH_2EtChBu^n)_2]_2$ and $Ti(OCH_2CH_2O)[OP(O)(OCH_2EtCHBu^n)_2]_2$ have been applied as coatings to carbon fibres to protect them against thermal oxidation. The action is due to the formation of a surface layer of TiO_2 on the fibre.[10]

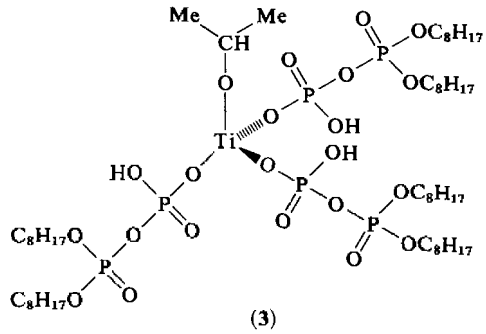
The properties of many polymers are improved by mixing them with an inorganic 'filler' (*e.g.* silica, alumina, calcium carbonate) and crosslinking agents are used to bond the organic polymer to the inorganic filler. Monte and Sugarman have described at length the requirements of such coupling agents.[11-17] They are generally tetrahedral titanium(IV) species containing an alkoxide ligand and three monodentate acid anions (**1**)–(**4**). The crosslinking action arises from the alkyl group of the acid residue being compatible with the organic polymer and the alkoxide group being displaced by an oxygen atom in the inorganic filler (monohydrolyzable titanates). The 2-propanolato group is frequently chosen as the alkoxide with carboxylate, sulfonate and phosphate anions such as isostearate, dodecylbenzenesulfonate and dioctyldiphosphate as acid residues. Tetraalkoxy titanium(IV) species are also used.[11]



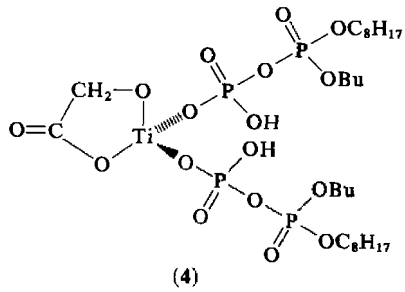
(1)



(2)



(3)



(4)

Titanate coupling agents have been found to offer corrosion resistance[12] and to give improved age and water resistance in reinforced plastics.[13] Their application in thermoplastics has been discussed in detail,[14,15] the requirements of a coupling agent have been established[16,17] and the theory of their use has been described.[18] A summary of the different types of structure, with examples, is available.[17]

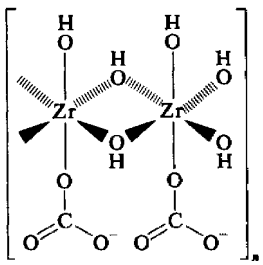
66.1.2 Zirconium and Hafnium

Zirconium hydride, ZrH_2, finds application as an antioxidant for rubber, in addition to being a moderator for nuclear fuel elements, and as a hydrogenation catalyst. Zirconium hydroxide, best formulated as $ZrO_2 \cdot nH_2O$ because of its variable water content, is used as a drying agent and absorbent and also has deodorant properties.[19]

Zirconium forms a wide range of fluoride complexes which have found application in improving the efficiency of synthetic grindstones, in metal–resin bonds for some printing plates, as a welding flux, as stabilizers for silicone rubber, in glass making, in dental plastics, in improving corrosion resistance and as a fluorinating agent.[20]

$ZrOCl_2$ is used by the oil industry in drilling operations to prevent damage to rock formations.[21] Its use for precipitation of phosphate ion from water as a means of controlling the growth of algae has also been reported.[22]

Ammonium zirconyl carbonate, $(NH_4)_3[ZrOH(CO_3)_3] \cdot 2H_2O$ is a constituent of flame-retarding systems used for cotton fabrics designed for outdoor use, such as tenting.[23] It is also employed as a water repellent in floor polishes and paper coatings, for the production of zirconium oxide films and as an adhesive in lithography.[20] The anion has a polymeric, hydroxide-bridged structure (**5**).



(**5**)

Trisglycolatozirconic acid, $H_3[ZrOH(OCH_2CO_2)_3]$, and its sodium salts have been used as body deodorants and as curing agents for silicone resins.[20] The analogous lactate, as the trisodium salt, is also used as a deodorant and as a flame retardant for paper.[19] The latter property depends on the lactate producing an extremely voluminous ash on burning, which inhibits further combustion. Zirconyl acetate, $H_2[ZrO_2(MeCO_2)_2]$, also imparts water repellent properties to textiles and finds application in curing silicone resins.[20]

Zirconium complexes have found worldwide use in increasing the flame resistance of wool (ZIRPRO process).[24] The fabric is treated with a hot aqueous mineral acid solution containing $ZrOCl_2$ and an α-hydroxy acid such as citric or tartaric acid. The nature of the species existing in the solution appears to be unknown, but α-hydroxycarboxylate chelates are thought to be involved.[25]

Tetraalkoxy zirconium complexes have been employed to improve the quality of rubber, but details of their structures do not seem to be available.[20]

Tetrakis(acetylacetonato)zirconium, which has a square antiprism structure, shows marked smoke-retarding properties in poly(vinyl chloride)[5] and it is effective as an accelerator in anhydride-cured epoxy resins.[26]

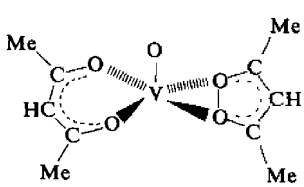
Zirconium carboxylates, generally referred to as 'zirconium soaps', are finding a wide range of applications. These include crosslinking in surface coatings and plastics, driers for alkyd paints and adhesion promoters in printing on to difficult surfaces.[27] Among the principal carboxylates involved are the octanoate, naphthenate, propionate, methacrylate and stearate. All are thought to have similar structures to the acetate, $H_2[ZrO_2(MeCO_2)_2]$.

Hafnium carbide has an extremely high melting point (3887 °C) and may find use as an alternative to tantalum carbide in the production of very hard metal components.[28]

66.2 VANADIUM, NIOBIUM AND TANTALUM

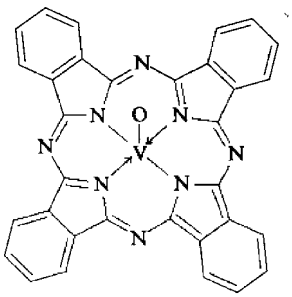
66.2.1 Vanadium

Vanadyl acetylacetonate (**6**) and vanadium pentoxide have been found to inhibit smoke formation in combustion tests on poly(vinyl chloride). The former is more active.[5]



(**6**)

In presence of triphenyl phosphite or tri(4-methyl-6-*t*-butylphenyl) phosphite, (**6**) also acts as an oxidation inhibitor for polyenes. The complexes formed have not been studied, but the effect is attributed to termination of radical chains and the complexes are more active than the phosphites alone.[29] Vanadyl acetylacetonate is also employed as a hardener for unsaturated polyesters.[30]



(7)

Vanadyl phthalocyanine (**7**) is effective as a smoke reducer for various styrene polymers.[31] Vanadyl sulfate, $VO(SO_4)_2$, finds application in the production of water resistant polymer foams.[32]

66.2.2 Niobium and Tantalum

Niobium pentoxide, Nb_2O_5, acts as a smoke retarder for poly(vinyl chloride) but is less effective than V_2O_5. Tantalum pentoxide is even more limited and is unlikely to find application.[5]

Phosphinate complexes of tantalum have been used as fillers for special purpose high temperature laminates. They are polymeric species of the stoichiometry $[Ta(OPPh_2O)_2(OH)_3]_n$.[33]

66.3 CHROMIUM, MOLYBDENUM AND TUNGSTEN

66.3.1 Chromium

Oxides of chromium have found a wide range of applications. Those more relevant to this chapter are summarized in Table 1. The individual use is often dependent on the cation. A more detailed summary of these and other simple chromium compounds is available.[34] They are mainly concerned with dyeing, pigments and metal treatment, and the appropriate chapters of this volume should be consulted. $CrPO_4$ and CrF_3 in addition to colour uses have corrosion inhibiting properties. Sodium chromate is also employed in the oil industry in the production of additives designed to limit corrosion cracking in drilling operations.[34]

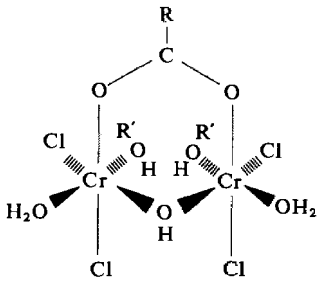
Table 1 Applications of Oxides of Chromium

Chromium compound	*Applications*
$[CrO_4]^{2-}$	Corrosion inhibition, printing, ceramics, pyrotechnics, metal priming and finishing, organic oxidation, gas absorbents, antifouling formulations
CrO_3	Fungicides (with CuO), organic oxidation, corrosion inhibition, catalysts (with CuO)
$[Cr_2O_7]^{2-}$	Ceramics, metal finishing, wood preservatives, corrosion inhibition, refractories, photosensitization
CrO_2Cl_2	Organic oxidation
CrO_2	Magnetic tapes, antifouling agents (with CuO)
$[Cr_2O_4]^{2-}$	Ceramics

Tris(acetylacetonato) chromium has been shown to be of interest as a smoke retarder for poly(vinyl chloride)[5] and it augments the inhibition of polyene oxidation by organic phosphites.[29]

Carboxylate complexes of chromium have been used in the paper industry as waterproofing and release agents for paper and paperboard.[35] The anions of myristic and stearic acids are commonly used. In alcoholic solution, the complexes are thought to have structure (**8**). During paper treatment, chain formation is thought to occur *via* oxide or hydroxide bridges, with the chloride being replaced by hydroxy groups in the paper.

Preparations containing chromium compounds are becoming increasingly important in the preservation of wood.[34,36] Damage to wood occurs principally through attack by microorganisms,



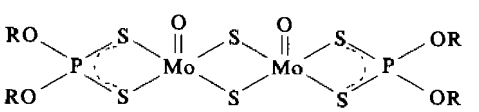
(8)

mainly fungi, through photolysis by the ultraviolet content of sunlight, by water, which causes hydrolysis, leaching and mechanical damage through swelling and shrinking, and by wood-boring insects. Early treatments involved chromium trioxide, sodium dichromate, copper chromate or ammoniacal copper chromate. Better results have now been achieved with preparations generally described as 'chromated copper arsenate' (CCA).[37] These comprise CrO_3, CuO and Na_2HAsO_4 and three mixtures of different composition are in use. Considerable chemical change occurs on treatment of the wood. CrO_3 is largely reduced to chromium(III) and species such as $[Cr(CrO_4)_3]^{3-}$ are thought to be involved. After about two weeks, some of the chromium and copper has been complexed by hydroxy and carboxylate groups in the wood. The binding of these hydrophilic groups reduces the extent of damage by water. The remainder of the copper and chromium is precipitated in the wood as, for example, $Cr(OH)_3$, $CrAsO_4$, CuOH and $CuAsO_4$. The absorption of UV light by the complexes present protects the wood against photolytic degradation. The fungicidal activity of copper (see Section 66.8.1) and the toxicity of arsenic compounds presumably help to prevent attack by microorganisms and wood-boring insects. The excellent properties of CCA-treated wood and the increasing cost of the oil-based alternatives pentachlorophenol and creosote have led to a dramatic increase in its use in spite of reservations regarding its toxicity.[37]

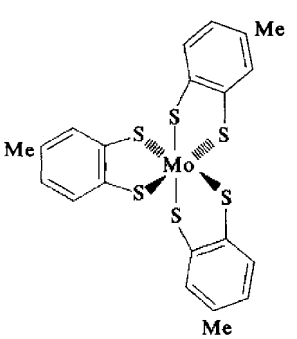
66.3.2 Molybdenum and Tungsten

Sodium molybdate is an important corrosion inhibitor. It is employed in cooling towers and in antifreeze (ethylene glycol) solutions. It is effective with cast iron, steel and aluminum and is also used in connection with the enamelling of steel.[38] Molybdates are also important as pigments and in dyeing (see Chapter 58). Molybdates act as flame retardants and smoke suppressors for poly(vinyl chloride). Best results appear to be obtained with $ZnMoO_4$, Zn_2MoO_5 and MoO_3.[5,39] In addition, $(NH_4)_2Mo_2O_7$ provides similar protection for cotton fabrics and may be used together with ammonium zirconyl carbonate (see Section 66.1.2) to this end.[23]

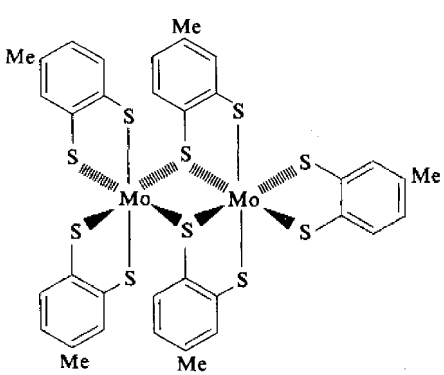
The introduction of molybdenum disulfide as a lubricant for machine parts has proved of great value. MoS_2 permits the 'running in' of moving parts by plastic deformation of their surfaces instead of the straightforward abrasion which occurs with organic lubricants.[38,40] The phosphorodithiolate (**9**) has been introduced commercially as a soluble molybdenum lubricant (R = alkyl group).[40] In addition the dithiolates (**10**) and (**11**) also showed excellent properties in testing, and may find application.[40]



(9)



(10)



(11)

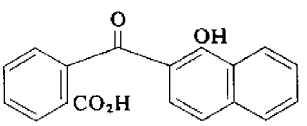
The principal uses of tungsten compounds lie outside the scope of this chapter (*e.g.* catalysts for oil refining). WS_2 is an effective additive for lubricating oils.[41] $CaWO_4$ is used as a phosphor for X-ray screens.[42] WO_3 is almost as effective as MoO_3 as a flame retardant for poly(vinyl chloride).[5]

66.4 MANGANESE, TECHNETIUM AND RHENIUM

A brief review of non-metallurgical uses of manganese compounds is available.[43] Most of them are not relevant to this chapter. Oxides of manganese are of great importance as a result of their oxidizing properties and low cost and they find many applications. The tetrahedral permanganate ion $[MnO_4]^-$, which as the potassium salt is manufactured on a very large scale,[44] and manganese dioxide are the most used oxides. MnO_2 prepared directly from the metal and oxygen has the octahedral rutile structure, but some methods of preparation lead to non-stoichiometric forms. In addition to chemical oxidation MnO_2, Mn_2O_3 and Mn_3O_4 are employed in connection with the electrical and electronics industries, in metallurgy, as colouring agents and in the production of magnetic materials, and the relevant chapters of this volume should be consulted. Many simple manganese salts are also used to these ends.[45] Potassium permanganate, in addition to being an oxidant in chemical manufacture, is used in the purification of drinking water, in the treatment of industrial wastes and effluents, in the bleaching of waxes and fibres and for the control of water quality in fisheries.[45]

The drastic increase in the price of oil led to the use of cheaper grades for electricity generation, providing new problems regarding combustion and effluent gases. The addition of oxides of manganese to fuel oils improves combustion efficiency and reduces smoke formation. Together with magnesium oxide, they limit the problems arising from fly-ash formation and reduce acid emissions by removing sulfur trioxide as sulfate.[46]

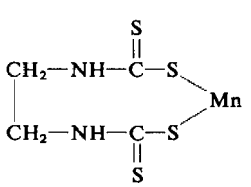
Manganese complexes of 2[(1-hydroxy-2-naphthalenyl)carbonyl]benzoic acid (**12**) are reported to be effective photostabilizers for polymers,[47] and manganese phthalocyanine shows smoke-retarding properties in polystyrene.[31]



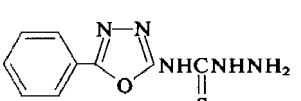
(**12**)

Bis(acetylacetonato)manganese shows smoke-retarding properties in poly(vinyl chloride) but Mn_2O_3 and $MnCO_3$ seem to be superior in this respect.[5] The so-called manganese 'soaps' having as anions octanoate, stearate, linoleate, naphthenate and others are used as driers (see Section 66.6.1) for printing inks, varnishes and paints.[45]

Manganese complexes are employed in agriculture as fungicides. By far the most important complex is 1,2-ethanediylbis(carbamodithioato)manganese (**13**) which is generally sold under the trade name 'Maneb'.[48] Its precise structure appears not to have been determined. Reports on its use in crop treatment are far too numerous to list here. It is applied either to the foliage directly or to the seed prior to planting. It can be used on many kinds of plants and trees but may cause injury to certain varieties of cherries, apples and tobaccos, to cucurbits and to tomato seedlings. It is toxic to fish.



(**13**)



(**14**)

Both the square planar bis(acetylacetonato)manganese(II) and the octahedral tris(acetylacetonato)manganese(III) have been shown to possess marked fungicidal activity in the protection of cotton and linen.[49] Recently, the complex of manganese(II) with 4-(5′-phenyl-1′,3′,4′-oxadiazol-2′-yl)thiosemicarbazide (**14**) has also been shown to exhibit fungicidal properties.[50] The structure of this bis-complex also appears to be unknown at present.

66.5 IRON, RUTHENIUM AND OSMIUM

66.5.1 Iron

Fe_3O_4 is employed to remove low concentrations of H_2S from natural gas (Slurrisweet Process).[51] Reactions (1)–(3) are thought to occur.

$$Fe_3O_4 + 4H_2S \rightarrow 3FeS + 4H_2O + S \quad (1)$$

$$FeS + S \rightarrow FeS_2 \quad (2)$$

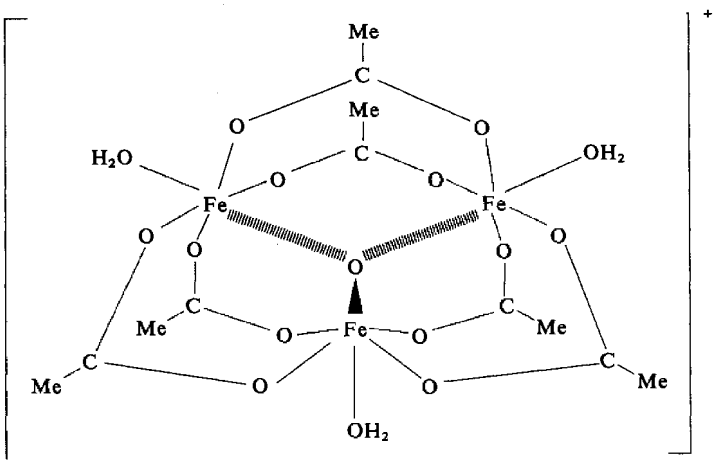
$$Fe_3O_4 + 6H_2S \rightarrow 3FeS_2 + 4H_2O + 2H_2 \quad (3)$$

Fe_2O_3 and Fe_3O_4 in presence of a chloride source act as flame retardants for nitrile-containing plastics and rubbers such as acrylonitrile–butadiene–styrene copolymers.[52] The activity appears to be connected with the formation of $FeCl_3$ on combustion, but other properties of $FeCl_3$ itself make it unsuitable for direct use. If an alkyl chloride is present iron(II) citrate may be used, and for halogen-containing nitrile polymers acetates, stearates, sulfates and carbonates are effective.

$FeCl_3$ is much used industrially and the other chapters of this volume should be consulted. It is employed as an oxidizing agent, as a Friedel-Crafts catalyst, for the etching of copper and zinc (printed circuits, photoengraving) and for etching without accompanying evolution of hydrogen. It is further used for the decolorizing of vegetable oils, in soap manufacture and in the purification of drinking water.[53] $FeCl_3$ has also been found to limit crystal size in the setting of cement.[54] Applications relevant to other chapters include dyeing, textile printing, pigments, metallurgy and medicine.

$[Fe(CN)_6]^{3-}$, as the free acid, has been used as a corrosion inhibitor for metal surfaces;[55] $K_2[Fe(CN)_6]$ has also been reported as being effective for this purpose.[56] Both hexacyano ions act as combustion inhibitors for aromatic polymers.[57] In the production of carbon monoxide by coke gasification for use in blast furnaces, additives are needed to enhance the reduction of any carbon dioxide formed back to the monoxide. Trisoxalatoiron has been found effective for this purpose.[58]

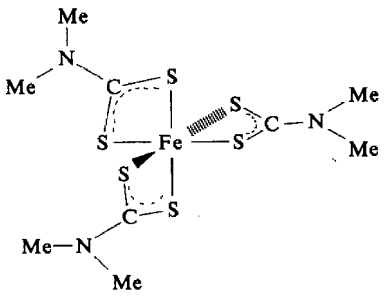
Boiling of a solution of iron(III) acetate produces a red-brown 'basic iron acetate' to which formulae such as $Fe(O_2CMe)_2OH$ have long been given. This material has been used for the weighting of silk, in addition to its applications in dyeing and printing.[55] The structure has been reinvestigated and found to be of the trinuclear[59] oxotrimetal type (**15**). In addition to $FeCl_3$ mentioned above, both $Fe_2(SO_4)_3$ and 'iron(III) hydroxide' are used as coagulants in water treatment, this time in the control of industrial effluent and sewage.[55] $FeSO_4 \cdot 7H_2O$ is one of the most important iron compounds. Its major use seems to be in the production of iron oxide pigments (see Chapter 58).[55]



(**15**)

Iron compounds are also effective smoke retarders for some polymers. Thus tris(acetylacetonato) iron, $FeSO_4$, $Fe_2(SO_4)_3$ and Fe_2O_3 are all roughly equal in combustion tests on poly(vinyl chloride).[5]

$Fe(S_2CNMe_2)_3$ (**16**) is an important fungicide sold commercially under the tradename 'Ferbam' (amongst others).[60] It has been in use for more than 50 years. As with the manganese fungicide Maneb (see Section 66.4), reports of its use in agriculture are far too numerous to list here. Ferbam is less phytotoxic than Maneb, though it causes russeting in one kind of apple. It can be used widely, with many fruits, vegetables, root crops and berries, as well as with melons, almonds and tobacco, and it controls a wide range of plant diseases. Ferbam should not be used in connection

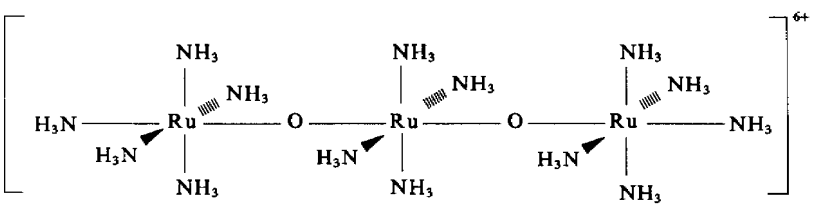


(16)

with lime of mercury or copper compounds. It is used together with Maneb and the zinc fungicide 'Ziram' (see Section 66.9.1). Another iron fungicide in use is the triammine methylarsonate sold under the trade name 'Neo-asozin'.[60] The stoichiometry of the compound is Fe[As(O)-(OH)Me]$(NH_3)_3$, but its actual structure does not appear to have been elucidated. Neo-asozin is of much more limited application than Ferbam, apparently being restricted to rice and grapes where it is used against sheath blight and ripe rot respectively. Its principal virtue seems to be that it does not exhibit the phytotoxicity observed when the free methylarsonic acid is used alone. On the other hand, it is toxic to fish even at low concentrations. It may be used in conjuction with other pesticides.[61] Because of the presence of arsenic, its use is now prohibited in many countries.

66.5.2 Ruthenium and Osmium

As with the other four platinum metals, the high cost of ruthenium and osmium limits their applications to those where a little goes a long way, such as catalysis and the plating of surfaces (see Chapters 57, 61 and 63). Ruthenium tetroxide has been used as a stoichiometric oxidizing agent in organic chemistry but is now much more commonly used in catalytic oxidations.[62] The so-called ruthenium red is used as a stain for electronmicroscopy and in optical microscopy it is the preferred stain for pectins.[63] It has been shown to have a linear trinuclear structure (17).[64] Tris(phenanthroline)ruthenium(II) possesses limited activity as a fungicide, but in view of its cost it is unlikely to find application as such.[65] Osmium tetroxide finds use in organic synthesis for the *cis*-hydroxylation of alkenes and catalytic methods have been developed. Its principal application relevant to this chapter is as a fixative and stain in electron microscopy.[62]



(17)

66.6 COBALT, RHODIUM AND IRIDIUM

66.6.1 Cobalt

Oxides of cobalt have been investigated as potential air deodorizing agents and for treatment of exhaust gases. They are also of interest as synthetic gems for use in bearings such as in wristwatches, and in connection with the manufacture of sulfuric acid.[66] In addition they find various applications in electronics (see Chapter 60). Mixed cobalt-molybdenum or cobalt-nickel-molybdenum oxides, or cobalt molybdates, are used in oil refining for cracking, hydrogenation, desulfurization and denitrification.[66]

$[Co(H_2O)_6]Cl_2$ and to a lesser extent other salts such as the thiocyanate have been used in desiccants to indicate the state of hydration,[66] and solutions of the chloride have been employed as invisible inks.

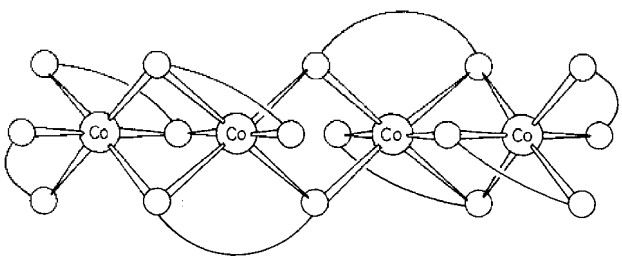
Bis(salicylaldehyde)diimine complexes of cobalt take up and release molecular oxygen with such efficiency that they have been made use of for the purification of oxygen.[66]

$K_3[Co(CN)_6]$ is important in the production of certain lasers.[66] Azides of cobalt ammines have been suggested as detonators, but appear to be inferior to lead and silver azides, which are in general use.[66]

A number of cobalt complexes are important as driers for the conversion of liquids to solids in inks, paints, varnishes and other surface coatings. The process is variously referred to as drying, curing or hardening. Most important in this respect are the cobalt 'soaps', which are complexes of carboxylate anions such as 2-ethylhexanoate, octanoate, oleate, linoleate, stearate, tallate and naphthenate. Thus cobalt octanoate and naphthenate have been investigated as driers for linseed oil on paper.[67] Cobalt naphthenate is also effective in drying urea-based resin coatings.[68] In order to achieve more rapid drying, cobalt(II)-ammine-β-diketonate complexes of the stoichiometry Co(β-diketonate)$_2$(ammine)$_2$ have been studied and found to be superior to the simple carboxylates. Ethyl acetoacetate and acetylacetonate were the preferred β-diketones, with morpholine, *N,N*-dimethylaniline and triethylamine as nitrogen ligands.[69]

Bis(acetylacetonato)cobalt(II) and tris(acetylacetonato)cobalt(III) have both been found to possess fungicidal activity on treated cotton and linen fabrics.[49] Both complexes have octahedral coordination about the metal, the cobalt(II) complex achieving this by forming a linear tetranuclear species (**18**). The latter complex is the somewhat more effective fungicide.

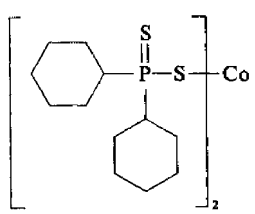
The introduction of steel cord into the manufacture of automobile tyres led to the need to find additives which would promote the adhesion of steel to rubber. A cobalt complex known commercially as 'Manobond C-16' has been used for this purpose.[70,71] Manobond C-16 is a borate complex with the composition $(RCO_2CoO)_3B$. The R groups are described as having an average of 21 carbon atoms, five of which are methyl groups.[72] No further structural details seem to be available.



(**18**)

(Reproduced with permission from F. A. Cotton and G. Wilkinson, 'Advanced Inorganic Chemistry', 4th edn., Wiley, New York, 1980, p. 769)

Cobalt complexes find various applications as additives for polymers. Thus cobalt phthalocyanine acts as a smoke retardant for styrene polymers,[31] and the same effect in poly(vinyl chloride) is achieved with Co(acac)$_2$, Co(acac)$_3$, Co_2O_3 and $CoCO_3$.[5] Co(acac)$_2$ in presence of triphenyl phosphite or tri(4-methyl-6-*t*-butylphenyl) phosphite has been found to act as an antioxidant for polyenes.[29] Both cobalt acetate and cobalt naphthenate stabilize polyesters against degradation,[73] and the cobalt complex of the benzoic acid derivative (**12**) (see Section 66.4) acts as an antioxidant for butadiene polymers.[46] Stabilization of poly(vinyl chloride)–polybutadiene rubber blends against UV light is provided by cobalt dicyclohexyldithiophosphinate (**19**).[74] Here again, the precise structure does not appear to be known.



(**19**)

66.6.2 Rhodium and Iridium

The considerations of cost mentioned above (see Section 66.5.2) for the platinum metals are also applicable here. In connection with slow release pesticide compositions, the complexes $RhCl(PPh_3)_3$, $RhCl(O_2)(PPh_3)_3$, $IrCl(CO)(PPh_3)_2$ and $IrCl(CO)(O_2)(PPh_3)_2$ have been described as constituents of urea–polysiloxane coatings for the active ingredient.[75] Other applications appear limited to plating and, of great importance, catalysis.

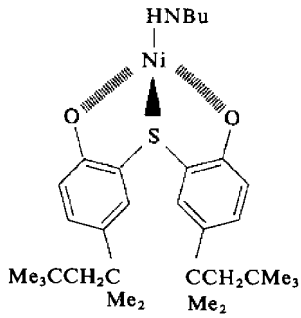
66.7 NICKEL, PALLADIUM AND PLATINUM

66.7.1 Nickel

Nickel compounds are of great importance industrially and a review is available on the use of nickel in heterogeneous catalysis, electroplating, batteries, pigments, ceramics and hydrogen storage.[76] This concerns simple aqua complexes of nickel(II) with anions such as carbonate, halide, hydroxide, nitrate and sulfate. Nickel acetate and formate find similar use, and the acetate is employed in the sealing of anodized aluminum.[77] $[Ni(NH_3)_6]Cl_2$ has been shown to be potentially applicable in heat pumps.[78]

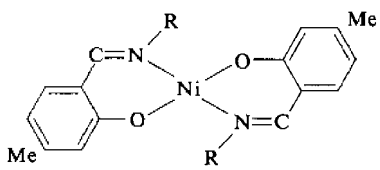
The dithiobenzil complex $[Ni\{4\text{-}Me_2NC_6H_4C(S)C(S)C_6H_4\}_2]$ has been used in laser technology.[79] Mode locking of lasers with this complex makes possible the production of light pulses of very short duration and high energy.[80]

Nickel complexes are of considerable importance as stabilizers and antioxidants for polymers of various kinds. The nickel(II) complex of the benzoic acid derivative (**12**) (see Section 66.4) acts as a stabilizer against oxidation of polybutadiene,[46] but is less effective in this respect than the manganese and cobalt complexes. Complex (**20**) is effective in decreasing the rate of photo-oxidation of two-phase poly(vinyl chloride)-polybutadiene rubbers.[74]

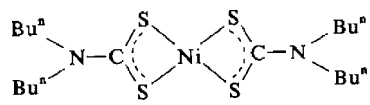


(**20**)

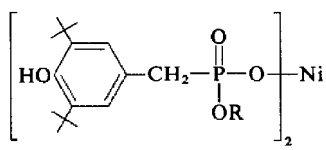
In addition to (**20**), complexes (**21**) and (**22**) act as stabilizers for polypropylene against photodegradation by UV light. The effect is believed to be partially due to quenching of excited states of carbonyl groups present as impurities in the polymer, but since no simple relationship between quenching ability and photostabilization was found the stabilizing action must be more complex than this and free radicals are thought to be involved.[81] Although bis(salicylaldiminato)nickel(II) complexes are normally planar, some distortion presumably arises from the presence of the large alkyl groups on the nitrogen atoms. In a further investigation involving polypropylene stabilized with complexes (**23**), (**24**) and (**25**), photodegradation was more pronounced in presence of oxygen than in its absence. The dithiocarbamate complex (**23**) was significantly the more active. Here again, free radicals were implicated in the degradation process.[82] The precise structures of complexes (**24**) and (**25**) do not appear to be known.



(**21**) R = Bu^n
(**22**) R = $C_{11}H_{23}$

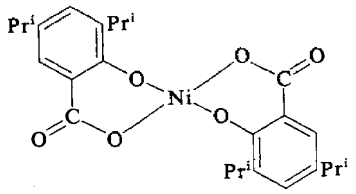


(**23**)

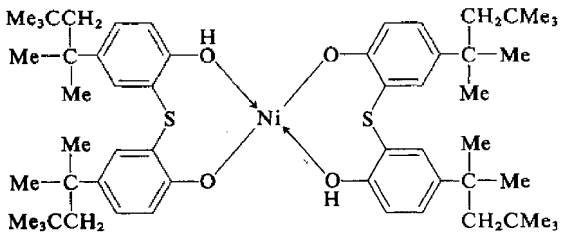


(**24**) R = Bu^n
(**25**) R = Et

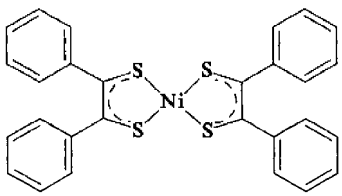
In addition to acting as photostabilizers for polypropylene, nickel complexes also inhibit their direct thermal oxidative degradation by molecular oxygen. The salicylate complex (**26**), thought to be square planar, was more effective than the analogous cobalt(II) and copper(II) complexes.[83] Iron(III) and chromium(II) analogues were almost inactive. Complexes (**25**) and (**27**) were roughly



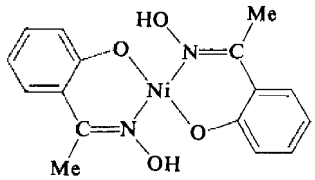
(26)



(27)



(28)

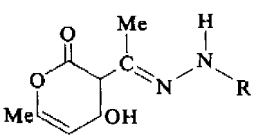


(29)

as effective as (**26**), whereas (**23**) was less active. By far the best stabilizer in this study was the stilbenedithiolate complex (**28**). Once again, the precise geometry of these complexes does not appear to be known.

The mechanism of the UV stabilization of high-density polyethylene by nickel complexes has been studied.[84,85] The stabilizing action may be caused by absorption of UV light by the complex, by the non-radical decomposition of hydroperoxides, or by the quenching of excited states which might directly or *via* energy transfer to oxygen give rise to species which may attack the polymer. The complexes studied were (**20**), (**23**) and (**29**). All three contribute towards stabilization of the polymer by absorbing UV light, but in addition some show some other effect. Thus the dithiocarbamate complex (**23**) promotes the decomposition of peroxides, and the oxime complex (**29**) undergoes stoichiometric reactions with hydroperoxides which are of a non-radical nature. Complex (**23**) is also of interest in the stabilization of acrylonitrile–butadiene–styrene copolymers and acts as an inhibitor of both photolytic and thermal oxidative degradation of high-impact polystyrene.[86,87] The analogous bis(diethyldithiocarbamato)nickel acts together with a UV absorber and a radical trap as a synergistic antioxidant for low-density polyethylene.[88] The function of the dithiocarbamate complex is again peroxide decomposition.

A number of nickel complexes have been shown to possess fungicidal activity. Salicylic acid complexes of the type $Ni(salicylate)_2(amine)_2$ have been tested on a range of fungi. They were active quite generally and in many cases the amine complexes were more active than diaquabis(salicylato)nickel. The amines used were pyridine, β-picoline, 8-hydroxyquinoline and nicotinic acid.[89] Nickel complexes of the Schiff bases (**30**), (**31**) and (**32**) were found to show both fungicidal and bactericidal activity, being effective against *Sarocladium oryzae* and *Xanthomonas oryzae*, which cause sheath rot and bacterial leaf blight in the rice plant. The complexes were found to be many times more active than the free ligands.[90]

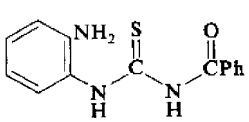


(**30**) R = —C(=O)Ph

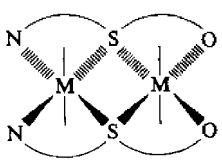
(**31**) R = —C(=O)C$_6$H$_4$OH-*o*

(**32**) R = —C(=S)NH$_2$

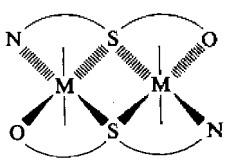
Complexes of *N*-benzoyl-*N'*-(2-aminophenyl)thiocarbamide (BAPTC) (**33**) having the stoichiometry $Ni_2X_4(BAPTC)_2$ ($X = Cl^-, Br^-, NO_3^-, ClO_4^-$) have been shown to exhibit antifungal activity against *Aspergillus niger*, *Fusarium oxysporium* and *Helminthosporium oryzae*.[91] The structure proposed is shown schematically as (**34**), the anions occupying the vacant coordination sites. The alternative structure (**35**) does not seem to have been considered, but would appear more likely on grounds of symmetry.



(33)

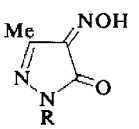


(34)

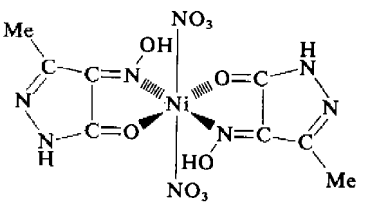


(35)

The organisms *Pyricularia oryzae*, which causes rice blast, and *Helminthosporium oryzae*, which causes brown leaf spot, can be controlled with complexes of the ligands 1-phenyl-3-methyl-4-nitroso-2-pyrazolin-5-one (**36**) and 3-methyl-4-nitroso-2-pyrazolin-5-one (**37**). The complexes were of the type ML_2X_2 (L = **36**, **37**: X = Cl^-, Br^-, NO_3^-) or $[ML_2]Y_2$ (Y = ClO_4^-). The former were assigned an octahedral or distorted octahedral structure and the latter are tetrahedral. The most active nickel complex was (**38**).[92]

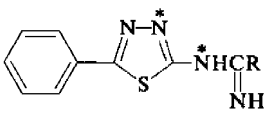


(**36**) R = Ph
(**37**) R = H



(**38**)

Six-coordinate thiadiazole complexes of the type $NiL_2(H_2O)_2$ (L = **39**, **40**) showed fungicidal activity against *Rhizopus nigracans* and *Curvularia lunata* and were more active than the free ligands. Bonding appears to be through the two nitrogen atoms designated with asterisks, as judged by the IR spectra.[93]



(**39**) R = Me
(**40**) R = Ph

66.7.2 Palladium and Platinum

The considerations of cost mentioned for the other four platinum metals above apply here also. There appear to be no applications of palladium relevant to this chapter.

$Ba[Pt(CN)_4]$ is used in the production of fluorescent X-ray screens.[94] Dichlorodihydroxy-diamine- and dichlorodinitratodiamine-platinum(IV) complexes show weak fungicidal activity, but there appears to be no likelihood of them actually being used to this end.[95] Other applications of platinum complexes involve their use as anticancer agents, as selective stains in biology, in catalysis, in metallurgy and in photography, described in the relevant chapters of this volume.

66.8 COPPER, SILVER AND GOLD

66.8.1 Copper

The applications of copper complexes are extremely varied and of great importance. Many of them are relevant to other chapters of this volume. Of those pertaining to this chapter, the two most important areas are polymer additives and, particularly, fungicides. The latter may be divided into four main areas: crop protection, the protection of wood and that of cotton, and their use in antifouling paints.

Cu_2O is used as an antioxidant in lubricants, as an absorbent for carbon monoxide and in helium purification. CuO is a constituent of antifouling paints and is used as a catalyst. $Cu(OH)_2$ finds application as a plastics stabilizer, in rayon production, and in antifouling paints. Mixed copper–chromium oxides are important as catalysts in a variety of processes and as wood preservatives (see Section 66.3.1). $Cu(NO_3)_2$ or its hydrates are employed in the oil industry as mud dispersants in drilling and as corrosion inhibitors, catalysts and wood preservatives. $CuSO_4 \cdot 5H_2O$ is the largest volume copper compound. It is important as a fungicide, but its main use is as the starting material for the preparation of other copper compounds.[96]

CuCl is used in lubricants, as a stabilizer for polymers, as a decolorizer for ceramics and as an antioxidant.[96] $CuCl_2$ is of interest as a preservative for wood, though copper oxides appear more important in this respect.[37] $CuBr_2$ finds application as a stabilizer for polymers and as a constituent of cutting fluids in machining. CuI is of potential interest in the initiation of rainfall by cloud seeding and in the production of conducting films. All the copper halides are of importance as catalysts for organic reactions.[96]

$Cu_2(O_2CMe)_4(H_2O)_2$, which has the binuclear tetraacetate bridged structure typical of a number of metal(II) acetates, is a stabilizer for various polymers. Copper(II) gluconate, $Cu[O_2C\{CH(OH)\}_4CH_2OH]_2$, is used as a deodorant. Copper(II) soaps, mainly the oleate and stearate, find application in antifouling paints, and as fungicides for textiles. A summary in tabular form of all applications of simple salts and complexes of copper is available.[96]

Table 2 Simple Copper Fungicides

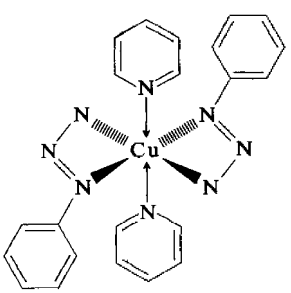
Trade names	*Composition*	*Date of introduction*
Bordeaux mixture	$CuSO_4 + Ca(OH)_2$	*ca.* 1885
Bluestone, blue copperas	$CuSO_4 \cdot 5H_2O$	Early 1800s
Neutrocop, spray cop	$CuSO_4 \cdot H_2O$	1807
C—O—C—S, copro 53	$(3Cu(OH)_2 \cdot CuCl_2) + 3Cu(OH)_2 \cdot CuSO_4)$	1945
Blitox, cobox and many others	$3Cu(OH)_2 \cdot CuCl_2$	*ca.* 1900
Basicop, copper 5 dust	$CuSO_4 \cdot 3Cu(OH)_2 \cdot H_2O$	1932
Blue shield, kocide	$Cu(OH)_2$	1960
Cuprocide, perecot and many others	Cu_2O	1932
Malachite, kop karb	$Cu(OH)_2 \cdot CuCO_3$	1887
Sol kop 10, taytox	'Copper ammonium carbonate' (structure unknown)	1887
Zinc coposil, citrusperse	'Basic copper sulfate' + 'basic zinc sulfate' or ZnO	—
Citcop, copoloid	Copper carboxylates	1964

Various mixtures of simple copper compounds with one another or with other compounds have been, and in some cases still are, of great importance as fungicides in agriculture. The range of plants on which they can be used and the diseases they control are too numerous to mention here and the literature should be consulted.[60] Table 2 gives the compositions of these mixtures and the more common trade names under which they are known.

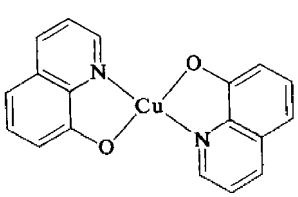
Bis(acetylacetonato)copper has been used as a source of copper in copper-vapour lasers,[97] and it has been investigated as a substitute for silver iodide as an ice-nucleating agent for the initiation of rainfall.[98]

The complexes $[Cu(S_2CNEt_2)_2]$ and $[Cu\{S_2P(OPr^i)_2\}_2]$ have been shown to be extremely effective scavengers for peroxy radicals and can be used to inhibit the autoxidation of hydrocarbons.[99] Poly(2,6-dimethyl-1,4-phenylene oxide) can be effectively stabilized against thermal degradation by the bistriazene complex (**41**).[100] The stabilizing action is thought to involve quenching of thermally excited states and the decomposition of hydroperoxides by the complex.

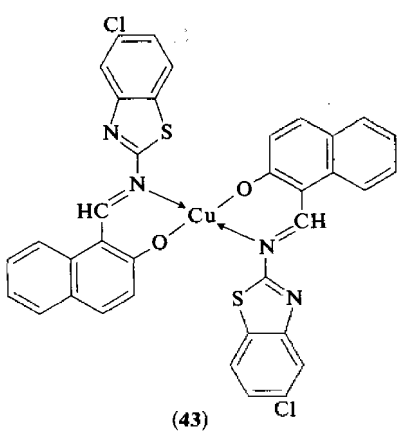
Copper phthalocyanine is more effective as a smoke retardant for polystyrene than most such complexes of the first row transition metals.[31] Other copper compounds which are effective smoke retardants for poly(vinyl chloride) are Cu_2O, CuO, CuI and $CuSO_4$.[5,101]



(41)



(42)



(43)

In addition to the copper fungicides mentioned above, a number of copper complexes are of importance. Thus bis(8-hydroxyquinolinato)copper (**42**) is used in the protection of fabrics, mainly cotton, against fungicidal attack. It is useful for fabrics which are much exposed to the weather, such as tenting.[60,102,103] Bis(acetylacetonato)copper is employed for the same purpose on cotton and linen fabrics.[49] Copper naphthenate is used both to protect fabrics and as a wood preservative.[60,104] The use of 'chromated copper arsenate' as a wood preservative has already been described (see Section 66.3.1). Ammonia-containing preparations have also been used, but little appears to be known about the complexes involved.[105] Copper complexes of the ligand *N*-benzoyl-*N'*-(2-aminophenyl)thiocarbamide (**33**) are effective fungicides for *Aspergillus niger*, *Fusarium oxysporium* and *Helminthosporium oryzae*.[91] They are said to have the structure (**34**) but see Section 66.7.1.

A number of benzothiazole–Schiff base complexes of the type (**43**) have been evaluated against *Helminthosporium oryzae*. Complex (**43**) and its zinc analogue were found to show enhanced activity relative to the free ligand.[106] The activity was very dependent on the substituent in the benzothiazole ring. Some analogous 4-phenylthiazole complexes of both metals were also effective,

the 4-(4-chlorophenyl)thiazole derivatives being the best of this type, though still inferior to the better benzothiazoles.[106]

In addition to the nickel complexes (**38**) already described, copper complexes of the pyrazolinone ligands (**36**) and (**37**) are effective against the same fungi (see Section 66.7.1.[92] Chloride or nitrate were the anions in the copper complexes.

Other copper compounds showing marked fungicidal activity, but whose precise structures do not appear to have been determined, are summarized in Table 3. Some reports of copper fungicides where even less is known about their coordination chemistry are available.[111–113] Copper complexes of the type $[Cu(salicylate)_2(amine)_2]$ analogous to the nickel complexes already mentioned (see Section 66.7.1) are reported to be more active fungicides than similar iron, cobalt and nickel complexes.[89] The same applies to copper complexes of the ligands (**30**), (**31**) and (**32**) compared with their manganese, iron, cobalt, nickel and zinc analogues.[90]

66.8.2 Silver and Gold

The principal use of silver compounds is in photography (see Chapter 59). The β-form of AgI is isomorphous with ice crystals, and it has been long used to initiate rainfall by serving as nuclei for crystallization of water. Ammoniacal solutions of silver(I) are used to prepare silver mirrors,[114] and AgN_3 has limited application as a detonator.[115] AgCl is used in self-darkening sunglasses. A high light intensity causes formation of silver metal, darkening the glass, which clears again as transparent AgCl is reformed in more subdued light.[116]

Silver salts, particularly $AgNO_3$ and $[Ag(S_2O_3)_2]^{3-}$, are used to preserve cut flowers.[117] The effect is associated with the inhibition of ethylene production in the flower.

An ethylenediaminetetraacetate complex of silver has been reported as being useful in fixing and developing fingerprints.[118]

Gold complexes of alkyl phosphonates and ammonia are additives for high pressure organic lubricants. Their precise structure does not seem to be known.[119] Solutions of $Na[AuCl_4] \cdot 2H_2O$ are used in electrodeless gold plating.[120]

A review of the applications of silver and gold is available.[62]

66.9 ZINC, CADMIUM AND MERCURY

66.9.1 Zinc

ZnO is of considerable commercial importance and applications relevant to this chapter include a variety of uses in the rubber industry as a curing accelerator, adhesive and stabilizer. It is also important in the manufacture of other zinc compounds and is increasingly being used in photocopying.[121] For its applications as a pigment see Chapter 58. ZnS is an important phosphor. Zinc borate is used in fireproofing fabrics and in fire-retarding paints.[121]

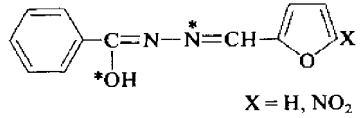
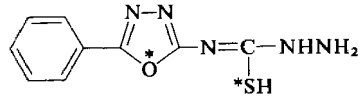
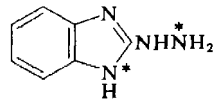
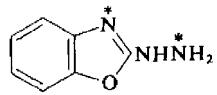
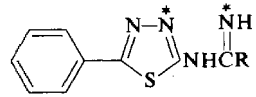
$ZnCl_2$ is important in vulcanizing rubber, in chemical synthesis, for fireproofing wood, in paper making, in treatment of fabrics and as a deodorant. $(NH_4)_2[ZnCl_4]$ is used as a flux for soldering and welding. A fluorosilicate, $ZnSiF_6 \cdot 6H_2O$, is employed as a wood preservative. $ZnSO_4$ is important in the manufacture of rayon, and is also a wood preservative.[121] A summary in tabular form of the applications of simple zinc compounds and complexes has appeared.[122]

Zinc soaps, which are complexes of long chain fatty acids, find similar applications in the curing and hardening of coatings to other transition metal soaps. A summary is available.[123] The more important anions are 2-ethylhexanoate, naphthenate and stearate. Mixtures of zinc and calcium soaps are also effective stabilizers for poly(vinyl chloride).[124] The complexes $[Zn\{OP(O)(OBu^n)_2\}_2]$ and $[Zn\{SP(S)(OBu^n)_2\}_2]$ both promote antiwear properties of lubricating oils.[125]

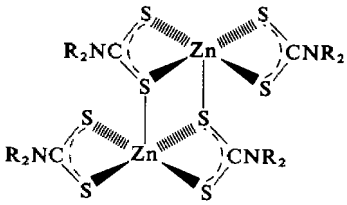
Zinc complexes are important as additives for rubber polymers. Dithiocarbamate complexes are most commonly used here, but bis(8-hydroxyquinolinato)zinc inhibits the thermal decomposition of poly[(trifluoroethoxy)(octafluoropentoxy)phosphazene]. The zinc is thought to complex residual P—OH groups in the polymer chain, which would otherwise lead to rearrangement and chain scission.[126]

The dithiocarbamates have the pentacoordinate binuclear structure (**44**). The diamyl- and diethyl-dithiocarbamate complexes have been found to inhibit the hardening of asphalt, but the effect appears too weak to be useful.[127] The latter complex is an effective antioxidant for polyethylene,[128] polypropylene,[129] polystyrene,[130] poly(methyl methacrylate)[130] and an isoprene–styrene copolymer.[131] The di-n-butyldithiocarbamate complex is important in the vulcanization and injection moulding of rubber,[132] as a stabilizer against photolytic and thermal degradation.

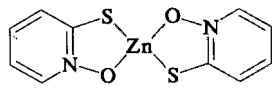
Table 3 Some Other Fungicidally Active Copper Complexes

Complex	*Ligand*[a] *(L)*	*Predicted geometry*	*Fungi treated*	*Ref.*
CuL_2	 X = H, NO_2	—	*Rhizoctonia solani*	107
CuL_2		Square planar	*Paccilomyces variotii* *Curvularia lunata*	108
$CuL_2(H_2O)_2$		Distorted octahedron	*Aspergillus niger* *Aspergillus flavus*	109
$[CuL_2(H_2O)_2](OAc)_2$		Distorted octahedron	*Aspergillus niger* *Aspergillus flavus*	109
$CuL_2(H_2O)_2$	 R = Me, Ph	Distorted octahedron	*Rhizopus nigracans* *Curvularia lunata*	110

[a] Ligating atoms marked with asterisk.



(44)



(45)

of styrene–butadiene–styrene copolymer thermoplastic rubbers[133] and as an inhibitor of the photodegradation of urethane polymers.[134]

The two most important zinc fungicides for crop protection are bis(dimethyldithiocarbamato)zinc (trade name 'Ziram') and ethylene-1,2-bis(dithiocarbamato)zinc (trade name 'Zineb'),[135] which is the zinc analogue of Maneb (see Section 66.4). Both are broad spectrum fungicides, applied to the leaf.

The zinc analogue of complex (**38**) is effective against *Pyricularia oryzae* and *Helminthosporium oryzae*,[92] and the zinc analogue of complex (**42**) is active against the latter organism.[106]

The pyridine oxide thiol complex (**45**) has been used as a fungicide in wood protection.[136]

66.9.2 Cadmium and Mercury

Simple cadmium compounds find application in many areas and the other chapters of this volume should be consulted. The more important of these uses appear to be as semiconductors and in various forms of colorizing agents.

CdO is used in connection with the stabilization of poly(vinyl chloride). This is discussed below in more detail. It also finds application in modifying the thermal properties of teflon and some rubbers. CdS is used in some smoke detectors, in lasers and in phosphors. The cadmium(II) halides are important as catalysts and are also used in pyrotechnics. Cadmium borates of the general type $(CdO)_x(B_2O_3)_y$ are also used as phosphors. $CdSO_4$ is employed in the Weston cell, which is important as a voltage standard.[137]

Cadmium soaps are of considerable importance in the stabilization of poly(vinyl chloride). The principal carboxylate anions used are laurate, myristate, palmate and stearate.[137] The polymer generally contains allylic chloride as a result of HCl elimination. As this leads to even more ready loss of HCl, polyene chains can arise which are susceptible to photolytic degradation. The cadmium soaps are thought to lead to substitution of the allylic chloride by a carboxylate anion, thus making the elimination far more difficult. They are generally used in presence of an excess of the barium salt of the carboxylate which serves to regenerate the cadmium soap from the $CdCl_2$ formed.[138,139] In some cases phosphites are added, but nothing seems to be known regarding the resulting complexes.[140]

Cadmium succinate is important as a fungicide and is used on turf to control a number of diseases.[141]

The toxicity of mercury compound has caused a drastic reduction in their use. They were once of considerable importance in agriculture and medicine but their use is now restricted in most parts of the world. Hence their use as fungicides in crop and seed protection is prohibited in many countries and the pharmaceutical applications are very limited.

The red form of HgO is of increasing importance in electronics in the production of miniature dry cells, and Hg_2SO_4 is employed in both the Weston and Clark standard cells. Hg_2Cl_2 still finds use as an antiseptic and HgI_2 is used to treat skin diseases. Mercury fulminate, $Hg(OCN)_2$, is an important detonator for explosives.[142]

Phenyl mercuric acetate was once used extensively as a general fungicide. Its use in agriculture has now been banned in many countries, though it appears that in some areas it is still used on turf and in seed treatment.[143] It was formerly used in antifouling paints for ships hulls, but here again it is now far less important. Its principal remaining application as a fungicide appears to be in latex paints.[142]

In spite of its toxicity, derivatives of phenyl mercuric acetate having substituents such as thiohydantoins in the aromatic ring are still being studied as fungicides and bactericides.[144–147]

66.10 SCANDIUM, YTTRIUM, LANTHANIDES AND ACTINIDES

Scandium does not appear to be put to any use relevant to this chapter. The applications of the actinides relate to their radioactivity and the appropriate chapters of this volume should be consulted.

La_2O_3 is used to produce glass having a high refractive index, from which optical fibres and lenses are made. CeO_2 is most important as a polishing agent for precision glassware such as lenses and the screens of television tubes, and is added to some glasses as a decolorizing agent.[148]

The lanthanides are important in the production of phosphors where they serve as activators. Europium in an yttrium oxide or orthovanadate screen fluoresces in the red, and such phosphors are used in colour television tubes. This is the largest scale use for an individual lanthanide element. In some applications (see below) advantage is taken of the similarity of their chemical properties by using mixtures of the lanthanides, thus reducing refining costs. Yttrium aluminum garnet has been employed to make artificial diamonds. Y_2O_3 is becoming increasingly important in the stabilization of ZrO_2 in ceramic thermal insulators, and YH_2 has excellent properties as a moderator in nuclear reactors.[148]

Nd_2O_3 doped into a glass or yttrium aluminum garnet is used as a laser. The neodymium is present only at low concentration. Such lasers can be operated at high average power levels, and continuously.[149] Neodymium pentaphosphate, $[Nd(P_5O_{14})]$, can be used without doping to produce miniature solid state lasers. The emission suffers no deterioration of radiative lifetime or linewidth and is ideal for continuous operation. The high neodymium concentration compared with the doped garnet lasers allows very short crystals to be used. $[Nd(P_5O_{14})]$ has each neodymium atom surrounded by eight oxygen atoms forming a dodecahedron, the metal atoms being linked through —O—P—O— bridges.[150]

The lanthanides find some use as stabilizers for polymers. The coating of polycarbonate with a poly(vinyl alcohol) film containing $CeCl_3$ inhibits photodegradation of the polycarbonate.[151] The naphthenates of cerium, lanthanum and yttrium act as thermal stabilizers for polyorganosiloxanes.[152]

Tetrakis(2,2,6,6-tetramethyl-3,5-heptanedionato)cerium(IV) has been found to have antiknock properties for petrol.[153] Other lanthanide complexes of the same ligand are also effective and mixtures may be used, especially those rich in cerium.[154]

Although they do not appear to have found application, lanthanide metal complexes of 8-hydroxyquinoline, 2-picolinic acid and catechol have been found to exhibit fungicidal properties.[155]

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$[Co(NH_3)_5(NCCH{=}CH_2)]^{3+}$, 449, 450
$CoC_3H_{18}N_7$
$[Co(NH_3)_5(\overline{N{-}CH{=}NCH{=}CH})]^{2+}$, 435
$CoC_3H_{20}N_6$
$[Co(NH_3)_4(HN{=}CMeCH_2NH_2)]^{3+}$, 458
$CoC_3H_{21}N_7$
$[Co(NH_3)_5(NCNMe_2)]^{3+}$, 449
$CoC_3H_{22}N_6$
$[Co(NH_3)_4\{NH_2CH_2CHMeNH_2\}]^{3+}$, 189
$CoC_3H_{22}N_6O$
$[Co(NH_3)_5(DMF)]^{3+}$, 433
$[Co(NH_3)_5(NH_2CH_2COMe)]^{3+}$, 189, 458
$CoC_3H_{24}N_5O_4P$
$[Co(NH_3)_5\{OP(OMe)_3\}]^{3+}$, 447
CoC_3NO_4
$Co(NO)(CO)_3$, 270
$CoC_3OH_{24}N_6$
$[Co(bipy)_3]^{3+}$, 652
$CoC_4H_2O_5$
$Co(O_2CCOCH_2CO_2)$, 455
$CoC_4H_6O_4$
$Co(OAc)_2$, 270
$CoC_4H_{13}Cl_3N_3$
$Co(dien)Cl_3$, 216, 436
$CoC_4H_{13}N_3$
$[Co(dien)]^{3+}$, 448
$CoC_4H_{13}N_6O_6$
$Co(dien)(NO_2)_3$, 436
$CoC_4H_{16}Cl_2N_4$
$[Co(en)_2Cl_2]^+$, 427
$CoC_4H_{16}N_3O_2$
$[Co(dien)(OH)(H_2O)]^{2+}$, 432
$CoC_4H_{16}N_4O_4P$
$Co(en)_2(PO_4)$, 446, 447
$CoC_4H_{17}N_4O_7P_2$
$Co(en)_2(HP_2O_7)$, 448
$CoC_4H_{18}N_3O_3$
$[Co(dien)(OH)(H_2O)_2]^{2+}$, 432
$CoC_4H_{18}N_4O_5P$
$Co(en)_2(OH)(HPO_4)$, 446
$CoC_4H_{19}N_4O_2$
$[Co(en)_2(OH)(H_2O)^{2+}$, 432
$CoC_4H_{19}N_6O_4$
$[Co(NH_3)_4\{O_2CCMe(CH_2NO_2)NH_2\}]^{2+}$, 186
$CoC_4H_{24}N_6O_2$
$[Co(NH_3)_5(H_2NCH_2CO_2Et)]^{3+}$, 214, 430
$CoC_4N_4S_4$
$[Co(NCS)_4]^{2-}$, 802, 847
CoC_5HN_5
$[CoH(CN)_5]^{3-}$, 496, 497
CoC_5HN_5O
$[Co(CN)_5(OH)]^{3-}$, 435
$CoC_5HN_5O_2$
$[Co(OOH)(CN)_5]^{3-}$, 324
$CoC_5H_2N_5O$
$[Co(CN)_5(H_2O)]^{2-}$, 435
$[Co(CN)_5(H_2O)]^{3-}$, 236
$CoC_5H_{20}Br_2N_5$
$[Co(en)_2Br(H_2NCH_2Br)]^{2+}$, 430
$CoC_5H_{20}N_5O_3$
$[Co(NH_3)_5(O_2CCO\overline{CHCH_2CH_2})]^{2+}$, 468
$CoC_5H_{21}N_7O$
$[Co(NH_3)_5(Ac\overline{N{-}CH{=}NCH{=}CH})]^{3+}$, 435
$CoC_5H_{22}N_5O_4$
$[Co(NH_3)_5\{O_2CCO(CH_2)_3OH\}]^{2+}$, 468
$CoC_5H_{24}N_6O_2$
$[Co(NH_3)_3\{HN{=}CMeC(CH_2OH)_2NH_2\}]^{3+}$, 189
CoC_5N_5
$[Co(CN)_5]^{3-}$, 236, 237, 497
$CoC_6H_{12}N_3O_6$
$Co(O_2CCH_2NH_2)_3$, 207
$CoC_6H_{13}N_2O_6$
$Co\{O_2CCH_2)_2NCH_2CH_2NH_2\}(OH)(H_2O)$, 432
$CoC_6H_{17}ClN_4O_2$
$[CoCl(dien)(H_2NCH_2CO_2)]^+$, 433
$CoC_6H_{17}N_5O_4$
$[Co(dien)(H_2NCH_2CO_2)(NO_2)]^+$, 433
$CoC_6H_{18}Cl_2N_4$
$[Co\{(H_2NCH_2CH_2NHCH_2)_2\}Cl_2]^+$, 215, 436
$CoC_6H_{18}N_4$
$[Co\{H_2NCH_2CH_2NHCH_2)_2\}]^{3+}$, 448
$CoC_6H_{18}N_5O_4$
$Co(NH_2)(en)_2(C_2O_4)$, 190

$CoC_6H_{19}ClN_5$
[Co(en)(H_2NCH_2CH=$NCH_2CH_2NH_2$)Cl]$^{2+}$, 459
$CoC_6H_{19}ClN_5O$
[CoCl(dien)($H_2CH_2CONH_2$)]$^{2+}$, 433
$CoC_6H_{19}N_6O_6P$
[Co(NH_3)$_5$($O_3POC_6H_4NO_2$-4)]$^+$, 447
$CoC_6H_{19}O_6P_2$
CoH{P(OMe)$_3$}$_2$, 239
$CoC_6H_{20}BrN_6$
[Co(en)$_2$Br(H_2NCH_2CN)]$^{2+}$, 451
$CoC_6H_{20}ClN_5O_2$
[Co(en)$_2$Cl($H_2NCH_2CO_2$)]$^+$, 430
$CoC_6H_{20}ClN_6$
[Co(en)$_2$Cl(H_2NCH_2CN)]$^{2+}$, 451
$CoC_6H_{20}N_5O_2$
[Co(en)$_2$($H_2NCH_2CO_2$)]$^{2+}$, 207, 214, 427, 429, 430, 433, 466, 469
[Co(NH_3)$_3${$O_2CCMe(NH_2)CH_2C(Me)$=NH}]$^{2+}$, 186
$CoC_6H_{21}ClN_5O$
[Co(en)$_2$(H_2NCH_2CHO)Cl]$^{2+}$, 458
$CoC_6H_{21}N_4O_2$
[Co{($H_2NCH_2CH_2NHCH_2$)$_2$}(OH)(H_2O)]$^{2+}$, 214, 215, 431, 432
[Co{N($CH_2CH_2NH_2$)$_3$}(OH)(H_2O)]$^{2+}$, 432
$CoC_6H_{21}N_6O$
[Co(en)$_2$(H_2NCH_2CN)(OH)]$^{2+}$, 452
$CoC_6H_{22}BrN_6O$
[Co(en)$_2$Br($H_2NCH_2CONH_2$)]$^{2+}$, 433
$CoC_6H_{22}N_6O$
[Co(en)$_2$($H_2NCH_2CONH_2$)]$^{3+}$, 432, 452
$CoC_6H_{23}N_6O_2$
[Co(en)$_2$(OH)($H_2NCH_2CONH_2$)]$^{2+}$, 434
$CoC_6H_{24}N_6$
[Co(en)$_3$]$^{3+}$, 99, 191
CoC_6N_6
[Co(CN)$_6$]$^{3-}$, 822, 1018
CoC_6O_{12}
[Co(C_2O_4)$_3$]$^{3-}$, 496, 531, 652
$CoC_7H_{19}N_6O$
[Co(NH_3)$_5$(4-NCC_6H_4O)]$^{2+}$, 449
$CoC_7H_{20}N_5O_2$
[Co(en)$_2${$O_2CC(Me)$=NH}]$^{2+}$, 187
$CoC_7H_{20}N_5O_2S$
[Co(en){$H_2NCH_2CH_2NHSCH_2CH(NH_2)CO_2$}]$^{2+}$, 212
$CoC_7H_{20}N_6$
[Co(NH_3)$_5$(NCPh)]$^{3+}$, 449, 450, 453
$CoC_7H_{21}N_6O$
[Co(NH_3)$_5$(HNCOPh)]$^{2+}$, 449
$CoC_7H_{22}BrN_6$
[Co(en)$_2$($H_2NCH_2CH_2CN$)Br]$^{2+}$, 451
$CoC_7H_{22}N_5O_2$
[Co(en)$_2$($O_2CCHMeNH_2$)]$^{2+}$, 207
$CoC_7H_{22}N_5O_2S$
[Co(en)$_2${$H_2NCH(CO_2H)CH_2S$}]$^{2+}$, 212, 213
$CoC_7H_{22}N_5O_4$
[Co(NH_3)$_4${O_2CC=$NCMe(OH)CMe(OH)CH_2$}]$^{2+}$, 186
$CoC_7H_{22}N_6O$
[Co(NH_3)$_5$(H_2NCOPh)]$^{3+}$, 449
$CoC_7H_{23}ClN_5O_2$
[Co(en)$_2$($H_2NCH_2CO_2Me$)Cl]$^{2+}$, 427
$CoC_7H_{23}N_5O_2$
[Co(en)$_2$($H_2NCH_2CO_2Me$)]$^{2+}$, 436
[Co(en)$_2$($H_2NCH_2CO_2Me$)]$^{3+}$, 427, 436
$CoC_7H_{24}N_6O$
[Co(en)$_2$($H_2NCH_2CH_2CN$)(H_2O)]$^{3+}$, 451
[Co(en)$_2$($H_2NCH_2CH_2CONH_2$)]$^{3+}$, 451
[Co(en)$_2$($H_2NCH_2CONHMe$)]$^{3+}$, 432
$CoC_7H_{25}N_3O_3$
[Co{$H_2N(CH_2)_4NH(CH_2)_3NH_2$}($H_2O$)$_3$]$^{3+}$, 498
$CoC_8H_{14}N_4O_4$
Co(HDMG)$_2$, 238, 257, 510
$CoC_8H_{20}N_4O_4P$
Co(1,4,7,10-tetraazacyclododecane)PO_4, 447
$CoC_8H_{20}N_5O_3$
[Co(dien)$H_2NCH_2CONHCH_2CO_2$)]$^+$, 467
$CoC_8H_{20}N_6O_5$
[Co(dien)($H_2NCH_2CONHCH_2CO_2$)(NO_2)]$^+$, 433
$CoC_8H_{21}ClN_5O$
[CoCl{$H_2NCH_2CH_2NHCH_2CH_2N(COCH_2NH_2)CH_2$-$CH_2NH_2$}]$^{2+}$, 189
$CoC_8H_{21}N_4O_5P$
[Co(1,4,7,10-tetraazacyclododecane)(OH)(OPO_3)]$^-$, 447
$CoC_8H_{21}N_6O_2S$
[Co(en)$_2${$H_2NCH(CH_2SCN)CO_2$}]$^{2+}$, 213
$CoC_8H_{21}N_7O$
[Co(NH_3)$_5$(2-$NCC_6H_4CONH_2$)]$^{3+}$, 451
$CoC_8H_{22}N_5O_2$
[Co{($H_2NCH_2CH_2NHCH_2$)$_2$}($O_2CCH_2NH_2$)]$^{2+}$, 215, 429, 431
[Co{N($CH_2CH_2NH_2$)$_3$}($O_2CCH_2NH_2$)]$^{2+}$, 211
$CoC_8H_{22}N_7O_2$
[Co(NH_3)$_5$(2-$HNCOC_6H_4CONH_2$)]$^{2+}$, 451
$CoC_8H_{23}ClN_5O$
[Co{($H_2NCH_2CH_2NHCH_2$)$_2$}(H_2NCH_2CHO)Cl]$^{2+}$, 458
$CoC_8H_{23}N_6O_3$
[Co(en)$_2$($H_2NCH_2CONHCH_2CO_2$)]$^{2+}$, 432
$CoC_8H_{24}N_4O_2$
[Co(1,4,7,10-tetraazacyclododecane)(H_2O)$_2$]$^{3+}$, 447
$CoC_8H_{24}N_6O$
[Co(NH_3)$_5$(NH_2CH_2COPh)]$^{3+}$, 189
$CoC_8H_{25}ClN_5O_2$
[Co(en)$_2$Cl($H_2NCH_2CO_2Et$)]$^{2+}$, 428
$CoC_8H_{26}N_5O_4$
[Co(NH_3)$_4${$O_2CCH(NH_2)CH_2CO_2Bu^i$}]$^{2+}$, 477
[Co(NH_3)$_5$(O_2CCH=$CHCO_2Bu^i$)]$^{2+}$, 477
$CoC_8H_{26}N_6$
[Co(dien)$_2$]$^{3+}$, 53
$CoC_8H_{26}N_6O$
[Co(en)$_2$($H_2NCH_2CONMe_2$)]$^{3+}$, 432
$CoC_8H_{28}N_6O$
[Co(en)$_2$(H_2NMe)(H_2NCH_2COMe)]$^{3+}$, 458
$CoC_9H_{13}N_2O_8$
[Ni{N(CH_2CO_2)$_3$}($H_2NCH_2CO_2Me$)]$^-$, 418
$CoC_9H_{22}N_4O_5$
[Co(en)$_2${$O_2CCH(O)CH_2CO_2Me$}]$^+$, 476
$CoC_9H_{23}ClN_4O_3$
[Co{$H_2N(CH_2)_3NH_2$}$_2${$O_2CC(Cl)$=CH_2}(OH)]$^+$, 476
[Co{$H_2N(CH_2)_3NH_2$}$_2$(O_2CCH=$CHCl$)(OH)]$^+$, 476
[Co{$H_2N(CH_2)_3NH_2$}$_2$($O_2CCHClCH_2O$)]$^{2+}$, 476
[Co{$H_2N(CH_2)_3NH_2$}$_2${$O_2CCH(O)CH_2Cl$}]$^{2+}$, 476
$CoC_9H_{23}N_4O_5$
[Co(en)$_2$(O_2CCH=$CHCO_2Me$)(H_2O)]$^{2+}$, 476
$CoC_9H_{26}N_5O_6$
[Co(NH_3)$_4${$O_2CCH(NH_2)CH(CO_2Et)_2$}]$^{2+}$, 188, 468
[Co(NH_3)$_5${O_2CCH=$C(CO_2Et)_2$}]$^{2+}$, 468
$CoC_9H_{26}N_6O$
[Co{($H_2NCH_2CH_2NHCH_2$)$_2$}($H_2NCH_2CONHMe$)]$^{3+}$, 432
$CoC_9H_{27}ClN_5O_2$
[Co(en)$_2$Cl($H_2NCH_2CO_2Pr^i$)]$^{2+}$, 428
$CoC_9H_{27}N_5O_2$
[Co(en)$_2$($H_2NCH_2CO_2Pr^i$)]$^{3+}$, 428, 432, 436
$CoC_9H_{30}N_6$
[Co{$H_2N(CH_2)_3NH_2$}$_3$]$^{3+}$, 125
$CoC_{10}H_5N_2O$
[Co(2-cyano-8-quinolinolate)]$^+$, 453
$CoC_{10}H_{12}N_2O_8$
[Co{(O_2CCH_2)$_2$$NCH_2CH_2N(CH_2CO_2)_2$}]$^-$, 652
$CoC_{10}H_{14}O_4$
Co(acac)$_2$, 118, 1019
$CoC_{10}H_{22}N_5O_7P$
[Co(en)$_2$(OH_2)($O_3POC_6H_4NO_2$-4)]$^+$, 446
$CoC_{10}H_{23}ClN_5$

$Co(en)_2Cl(H_2NPh)$, 990

$CoC_{10}H_{23}N_7O_6$
[Co(dien)($H_2NCH_2CONHCH_2CONHCH_2CO_2$)-($NO_2$)]$^+$, 433

$CoC_{10}H_{25}ClN_5O_3$
[CoCl(dien)($H_2NCH_2CONHCH_2CO_2Et$)]$^{2+}$, 433

$CoC_{10}H_{25}N_6O_3$
[Co{($H_2NCH_2CH_2NHCH_2)_2$}-($H_2NCH_2CONHCH_2CO_2$)]$^{2+}$, 432

$CoC_{10}H_{25}N_6O_5$
[Co(dien)($H_2NCH_2CONHCH_2CO_2Et$)(NO_2)]$^{2+}$, 433

$CoC_{10}H_{25}N_8O_{13}P_3$
$Co(NH_3)_3ATP$, 447

$CoC_{10}H_{26}N_6O$
[Co([15]aneN$_5$)(OH)]$^{2+}$, 436

$CoC_{10}H_{27}ClN_5O_2$
[Co{($H_2NCH_2CH_2NHCH_2)_2$}Cl($H_2NCH_2CO_2Et$)]$^{2+}$, 429

$CoC_{10}H_{29}ClN_5O_2$
[CoCl{($H_2NCH_2CH_2NHCH_2)_2${H_2NCH_2-$CH(OMe)_2$}]$^{2+}$, 189

$CoC_{10}H_{30}N_6$
[Co{$MeC(CH_2NH_2)_3$}$_2$]$^{3+}$, 193

$CoC_{10}H_{30}N_6O_2$
[CO(en)$_2$(H_2NCH_2COMe)$_2$]$^{3+}$, 190

$CoC_{11}H_{19}N_4O_2$
[Co{ON=CMeC(Me)=N$(CH_2)_3$N=CMeC(Me)=NOH}]$^+$, 257

$CoC_{11}H_{22}N_5O_3$
[Co{$N(CH_2CH_2NH_2)_3$}{$O_2CCH(NH_2)CHO$}]$^{2+}$, 211

$CoC_{11}H_{24}N_5O_3$
[Co{$N(CH_2CH_2NH_2)_3$}{$O_2CCH(NH_2)CH_2OH$}]$^{2+}$, 211

$CoC_{11}H_{27}ClN_6O$
[Co{$N(CH_2CH_2NH_2)_3$}{$ClCOC(NH_2)$=CH-NMe_2}]$^{3+}$, 211

$CoC_{11}H_{28}N_6O_3$
[Co{($H_2NCH_2CH_2NHCH_2)_2$}-($H_2NCH_2CONHCH_2CO_2Me$)]$^{3+}$, 432

$CoC_{11}H_{30}N_6$
[Co{$MeC(CH_2NHCH_2CH_2NH_2)_3$}]$^{3+}$, 191, 192

$CoC_{12}H_{22}Cl_2N_4O$
[CoCl$_2${N=CMeCOC(Me)=N$CH_2CH_2NH(CH_2)_3$-$NHCH_2CH_2$}]$^+$, 168

$CoC_{12}H_{24}Cl_2N_4$
[CoCl$_2${N=CMeCH$_2$C(Me)=N$CH_2CH_2NH(CH_2)_3$-$NHCH_2CH_2$}]$^+$, 168

$CoC_{12}H_{30}N_6O_3$
[Co{($H_2NCH_2CH_2NHCH_2)_2$}($H_2NCH_2CONHCH_2$-CO_2Et)]$^{3-}$, 436

$CoC_{12}H_{30}N_8$
[Co(sepulchrate)]$^{3+}$, 507
[Co{$N(CH_2NHCH_2CH_2NHCH_2)_3N$}]$^{3+}$, 191

$CoC_{12}H_{32}N_6$
[Co{$MeC(CH_2NHCH_2CH_2NH_2)_2(CH_2NHCH_2$-$CH_2NHMe)$}]$^{3+}$, 192

$CoC_{12}H_{32}O_9P_3$
Co{$P(OMe)_3$}$_3$(η^3-C_3H_5), 238

$CoC_{13}H_{19}ClN_5O_4$
$Co(HDMG)_2Cl(py)$, 387

$CoC_{13}H_{32}N_6O$
[Co([15]aneN$_5$)(DMF)]$^{3+}$, 434

$CoC_{13}H_{32}N_6O_3$
[Co{$H_2NCH_2CH_2NHCH_2)_2$}-($H_2NCH_2CONHCH_2CO_2Pr^i$)]$^{3+}$, 432

$CoC_{14}H_{33}N_7$
[Co{$MeC(CH_2NHCH_2CH_2NHCH_2)_3N$}]$^{3+}$, 191

$CoC_{15}H_{21}O_6$
$Co(acac)_3$, 1019

$CoC_{15}H_{28}O_3P$
$CoH(CO)_3(PBu_3)$, 259

$CoC_{15}H_{33}N_7O_2$
[Co{$MeC(CH_2NHCH_2CH_2NHCH_2)_3CNO_2$}]$^{3+}$, 191

$CoC_{15}H_{34}N_6$
[Co{$MeC(CH_2NHCH_2CH_2NHCH_2)_3CH$}]$^{3-}$, 191

$CoC_{15}H_{34}N_6O$
[Co{$MeC(CH_2NHCH_2CH_2NHCH_2)_3COH$}]$^{3+}$, 191

$CoC_{15}H_{36}N_7$
[Co{$MeC(CH_2NHCH_2CH_2NHCH_2)_3CNH_3$}]$^{6+}$, 191

$CoC_{16}H_{14}N_2O_2$
Co(salen), 387, 388

$CoC_{16}H_{14}N_3O_3$
Co(NO)(salen), 372

$CoC_{16}H_{16}N_7O_{13}S_3$
[Co{1-O-2-(2-O-3-O_3S-5-$O_2NC_6H_2N$=N)-3,6-$(O_3S)_2$-8-$H_2NC_{10}H_3$}$(NH_3)_3$]$^{2-}$, 51

$CoC_{16}H_{16}O_3P$
Co$(CO)_3(PPh_2Me)$, 270

$CoC_{16}H_{20}ClN_4$
[Co(2-$Me_2NC_6H_4N$=$NC_6H_4NMe_2$)Cl]$^+$, 60

$CoC_{16}H_{20}N_8O_4$
[Co{2-O-5-$O_2NC_6H_3N$=NC=C(O)NPhN=CMe}-$(NH_3)_3$]$^+$, 52

$CoC_{16}H_{32}N_4$
[Co(Me$_6$[14]dieneN$_4$)]$^{2+}$, 509

$CoC_{17}H_{40}O_9P_3$
Co{$P(OMe)_3$}$_3$(η^3-C_8H_{13}}, 239

$CoC_{18}H_{16}O_4P$
Co(COMe)$(CO)_3(PPh_2Me)$, 270

$CoC_{18}H_{19}N_2O_2$
CoEt{2-(2-OC_6H_4CH=NCH_2CH_2N=CH)C_6H_4O}, 114

$CoC_{18}H_{19}N_8O_5S$
Co{HN=$C(NH_2)NHC(NH_3)$=N}{1-(2-O-5-$O_3SC_6H_3$-N=N)-2-$OC_{10}H_6$}(NH_3), 52

$CoC_{18}H_{29}N_7O$
[Co{$N(CH_2NN$=CMeCH=$CMe)_3$}(H_2O)]$^{2+}$, 601

$CoC_{19}H_{20}N_4$
Co{N=$CHC_6H_4N(CH_2)_3NC_6H_4CH$=$NCH_2CH_2$}, 176

$CoC_{20}H_{14}N_3O_3$
Co{1,2-(2-OC_6H_4CH=N)$_2C_6H_4$}(NO), 372

$CoC_{20}H_{18}N_6O_2$
[Co(O_2){(2-py)$_2$NH}$_2$]$^+$, 329

$CoC_{20}H_{20}N_2O_4$
[Co{{2-O-3-$(HOCH_2)$-5-$O_2NC_6H_2CH$=CH}-C=N(Me)$C_6H_4CMe_2$}]$^+$, 126

$CoC_{21}H_{24}N_3O_2$
Co{{2-OC_6H_4CH=N$(CH_2)_3$}$_2$NMe}, 387

$CoC_{22}H_{30}N_5O_6$
Co$(HDMG)_2$(py)$(OOCMe_2Ph)$, 330

$CoC_{24}H_{45}O_6$
Co{$O_2C(CH_2)_6Me$}$_3$, 386

$CoC_{25}H_{19}N_4O_4$
Co{1,2-(2-OC_6H_4CH=N)$_2C_6H_4$}(py)(NO_2), 372

$CoC_{25}H_{21}N_6$
Co(CN)$_2$(NCH=CPhCH=NCH=CHCH=NCH=CPhCH=NCH_2CH_2), 168

$CoC_{26}H_{55}O_2P_2$
$CoH(CO)_2(PBu_3)_2$, 238

$CoC_{27}H_{29}N_3O_4$
Co(O_2){{$PhCOCH_2C(Me)$=NCH_2}$_2$}(py), 320

$CoC_{27}H_{54}O_3P_2$
[Co$(CO)_3(PBu_3)_2$]$^+$, 259

$CoC_{28}H_{24}N_4O_4$
[Co(2-O-5-MeC_6H_3N=NC_6H_3Me-5-O-2)$_2$]$^-$, 63

$CoC_{29}H_{27}N_6$
[Co{N=CHC_6H_4NCH=CHCH=NC_6H_4CH=N-CH_2CH_2}(py)$_2$]$^{2+}$, 176

$CoC_{30}H_{15}N_3O_{15}S_3$
[Co(1-ON-2-O-6-$O_3SC_{10}H_{15}$)$_3$]$^{3-}$, 85

$CoC_{32}H_{16}N_8$
Co(phthalocyanine), 88, 1019

$CoC_{32}H_{18}N_6O_8$
[Co{1-(2-O-5-$O_2NC_6H_3N$=N)-2-$OC_{10}H_6$}$_2$]$^-$, 51

$CoC_{32}H_{19}N_8O_{11}S$

$[Co\{2\text{-}O\text{-}5\text{-}O_2NC_6H_3N{=}NC{=}C(O)NPhN{=}CMe\}\text{-}\{1\text{-}(2\text{-}O\text{-}3\text{-}O_3S\text{-}5\text{-}O_2NC_6H_2N{=}N)\text{-}2\text{-}OC_{10}H_6\}]^{2-}$, 52

$CoC_{32}H_{21}N_6O_8S_2$
$[Co\{1\text{-}(2\text{-}O\text{-}5\text{-}O_3SC_6H_3N{=}N)\text{-}2\text{-}OC_{10}H_6\}\{1\text{-}(2\text{-}H_2N\text{-}5\text{-}O_3SC_6H_3N{=}N)\text{-}2\text{-}HNC_{10}H_6\}]^{2-}$, 60

$CoC_{32}H_{22}N_4O_2$
$Co\{1\text{-}(PhN{=}N)\text{-}2\text{-}OC_{10}H_6\}_2$, 43

$CoC_{32}H_{22}N_6O_2$
$[Co\{1\text{-}(2\text{-}OC_6H_4N{=}N)\text{-}2\text{-}HNC_{10}H_6\}_2]^{-}$, 58

$CoC_{32}H_{24}N_6$
$Co\{1\text{-}(PhN{=}N)\text{-}2\text{-}HNC_{10}H_6\}_2$, 44

$CoC_{32}H_{26}N_8$
$[Co\{1\text{-}(2\text{-}H_2NC_6H_4N{=}N)\text{-}2\text{-}HNC_{10}H_6\}_2]^{+}$, 59

$CoC_{32}H_{32}N_6$
$[Co\{N{=}CMeCH{=}CMeC_6H_4N{=}CMeCH{=}CMeNC_6H_4\}(py)_2]^{+}$, 173

$CoC_{32}H_{68}O_8P_2$
$Co\{OP(O)(OCH_2CHEtBu)_2\}_2$, 792

$CoC_{34}H_{34}Cl_2N_4O_4$
$Co(2\text{-}O\text{-}3\text{-}Me\text{-}5\text{-}Bu^tC_6H_2N{=}NC_6H_3O\text{-}2\text{-}Cl\text{-}5)_2$, 67

$CoC_{36}H_{18}N_6O_{18}S_6$
$[Co\{4,7\text{-}(O_3S)_2phen\}_3]^{3-}$, 653

$CoC_{36}H_{19}N_6O_{11}S$
$[Co\{1\text{-}(2\text{-}O\text{-}5\text{-}O_2NC_6H_3N{=}N)\text{-}2\text{-}OC_{10}H_6\}\{1\text{-}(2\text{-}O\text{-}1\text{-}C_{10}H_6N{=}N)\text{-}2\text{-}O\text{-}4\text{-}O_3S\text{-}6\text{-}O_2NC_{10}H_4\}]^{2-}$, 51

$CoC_{36}H_{24}N_6$
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$[Co(phen)_3]^{3+}$, 652

$CoC_{36}H_{30}I_2P_2$
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$CoC_{37}H_{26}N_4P$
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$CoC_{38}H_{29}N_8O_2$
$Co\{2\text{-}OC_6H_4N{=}NC(Ph){=}NNPh\}\{2\text{-}HOC_6H_4N{=}NC(Ph){=}NNPh\}$, 81

$CoC_{38}H_{30}N_8$
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$CoC_{38}H_{32}Cl_2N_8$
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$CoC_{40}H_{20}N_6O_{14}S_2$
$[Co\{1\text{-}(2\text{-}O\text{-}1\text{-}C_{10}H_6N{=}N)\text{-}2\text{-}O\text{-}4\text{-}O_3S\text{-}6\text{-}O_2NC_{10}H_4\}_2]^{3-}$, 51

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$CoC_{42}H_{30}N_{13}$
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$CoC_{44}H_{28}N_4$
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$CoC_{48}H_{33}N_6O_3$
$Co\{1\text{-}(PhN{=}N)\text{-}2\text{-}OC_{10}H_6\}_3$, 43

$CoC_{49}H_{33}N_6O_2$
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$CoC_{52}H_{44}O_2P_4$
$[Co(O_2)(Ph_2PCH{=}CHPPh_2)_2]^{+}$, 321, 329

$CoC_{52}H_{49}P_4$
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$CoC_{54}H_{45}BrP_3$
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$CoC_{54}H_{45}ClP_3$
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$CoC_{64}H_{138}O_{16}P_4$
$Co\{OP(O)(OCH_2CHEtBu)_2\}_2\{HOP(O)(OCH_2CHEtBu)_2\}_2$, 793

$CoC_{72}H_{59}O_{12}P_4$
$Co\{C_6H_4OP(OPh)_2\}\{P(OPh)_3\}_3$, 238

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$CoH_{14}N_4O_{10}P_3$
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$CoH_{16}N_4O_2$
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$CoH_{16}N_5O_7P_2$
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$CoH_{17}N_5O$
$[Co(NH_3)_5(H_2O)]^{3+}$, 99, 188, 434, 468, 801

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$[Co(NH_3)_6]^{2+}$, 52, 801
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$[Cu(dien)(H_2NCH_2CO_2Me)]^{2+}$, 419
$CuC_8H_{11}NO_6$
$Cu\{EtO_2CCH_2N(CH_2CO_2)_2\}$, 422
$CuC_8H_{12}N_2O_6$
$Cu(O_2C\overline{CHNHCH_2OCH_2})_2$, 207
$CuC_8H_{12}N_8O_4$
$[Cu\{\overline{NNHCHMeNHNCOCONNHCHMe\text{-}NHNCOCO}\}]^-$, 181
$CuC_9H_9NO_4$
$Cu(2\text{-}OC_6H_4CH{=}NCH_2CO_2)(H_2O)$, 211
$CuC_9H_{13}N_2O_8$
$[Cu\{N(CH_2CO_2)_3\}(H_2NCH_2CO_2Me)]^-$, 418, 419
$CuC_9H_{20}N_3O_4$
$[Cu(H_2NCH_2CH_2NHCH_2CO_2)\{L\text{-}\alpha\text{-}MeCH(NH_2)CO_2Et\}]^+$, 418
$CuC_9H_{23}N_3O_2$
$[Cu(TMEDA)(H_2NCH_2CO_2Me)]^{2+}$, 419
$CuC_{10}H_{14}O_4$
$Cu(acac)_2$, 107, 203, 206, 1023
$CuC_{10}H_{15}N_2O_8$
$[Cu\{N(CH_2CO_2)_3\}(H_2NCH_2CO_2Et)]^-$, 418
$CuC_{10}H_{20}N_2S_4$
$Cu(S_2CNEt_2)_2$, 1023
$CuC_{10}H_{22}N_2O_2$
$Cu\{(OCH_2CHEtNHCH_2)_2\}$, 990
$CuC_{11}H_9Cl_2NO_2$
$CuCl_2$(8-acetoxyquinoline), 472
$CuC_{11}H_9N_2O_4$
$[Cu\{2\text{-}OC_6H_4CH{=}NCH_2C(O)NCH_2CO_2\}]^-$, 426
$CuC_{11}H_{10}N_2O_2S$
$[Cu\{SC(NHC_6H_4CO_2\text{-}3){=}NCH_2CH{=}CH_2\}]^-$, 760
$CuC_{11}H_{10}N_2O_4$
$Cu(2\text{-}OC_6H_4CH{=}NCH_2CONHCH_2CO_2)$, 213
$CuC_{11}H_{15}N_2O_8$
$[Cu\{O_2CCH_2)_2NCH_2CH_2N(CH_2CO_2Me)\text{-}(CH_2CO_2)\}]^-$, 423
$CuC_{11}H_{17}NO_6$
$Cu\{EtO_2CCH(CHMe_2)N(CH_2CO_2)_2\}$, 421
$CuC_{11}H_{20}N_5O_4$
$[Cu(H_2NCH_2CH_2NHCH_2CO_2)\{L\text{-}\overline{N{=}CHNHCH{=}C}\text{-}CH_2CH(NH_2)CO_2Me\}]^+$, 418
$CuC_{12}H_{12}N_2O_4$
$Cu\{2\text{-}pyCH(OH)O\}_2$, 474
$CuC_{12}H_{14}N_2O_2$
$[Cu\{2\text{-}pyCH{=}NPh\}(H_2O)_2]^{2+}$, 461
$CuC_{12}H_{16}N_2O_8$
$Cu\{O_2CC(CH_2OCH_2)_2N\}_2$, 207
$CuC_{12}H_{18}N_2O_8$
$Cu\{(O_2CCH_2)_2NCH_2CH_2N(CH_2CO_2Me)_2\}$, 423
$CuC_{12}H_{18}O_6$
$Cu(MeCOCHCO_2Et)_2$, 469
$CuC_{12}H_{20}N_2O_6$
$Cu(O_2C\overline{CHNHCHMeOCHMe})_2$, 207
$CuC_{12}H_{22}O_{14}$
$Cu\{O_2C(CHOH)_4CH_2OH\}_2$, 1022
$CuC_{12}H_{28}O_4P_2S_4$
$Cu\{S_2P(OPr^i)_2\}_2$, 1023
$CuC_{12}H_{36}O_{12}P_4$
$[Cu\{P(OMe)_3\}_4]^+$, 113
$CuC_{13}H_{11}N_2O_3$
$Cu\{2\text{-}(2\text{-}O\text{-}5\text{-}MeC_6H_3N{=}N)C_6H_4O\}(H_2O)$, 75
$CuC_{13}H_{21}N_2O_8$
$[Cu\{(MeO_2CCH_2)_2NCH_2CH_2N(CH_2CO_2Me)\text{-}(CH_2CO_2)\}]^+$, 423
$CuC_{14}H_9N_5O_2$
$Cu\{2\text{-}\{2\text{-}HOC_6H_4N{=}NC(CN){=}NN\}C_6H_4O\}$, 82
$CuC_{14}H_{10}O_4$
$Cu(2\text{-}OC_6H_4CHO)_2$, 157, 213, 426
$CuC_{14}H_{10}O_6$
$Cu(2\text{-}HOC_6H_4CO_2)_2$, 760
$CuC_{14}H_{12}N_2O_4$
$Cu(2\text{-}OC_6H_4CH{=}NOH)_2$, 800
$CuC_{14}H_{15}N_2O_4$
$Cu\{2\text{-}OC_6H_4CH{=}NCH_2CONCH(CHMe_2)CO_2\}$, 209
$CuC_{14}H_{22}N_3O_4$
$[Cu(H_2NCH_2CH_2NHCH_2CO_2)\{L\text{-}\beta\text{-}PhCH_2CH(NH_2)CO_2Me\}]^+$, 418
$CuC_{14}H_{24}N_2O_8$
$[Cu\{(MeO_2CCH_2)_2NCH_2CH_2N(CH_2CO_2Me)_2\}]^{2-}$, 423
$CuC_{15}H_{12}N_2O_4$
$Cu\{2\text{-}(2\text{-}O\text{-}5\text{-}MeC_6H_3N{=}N)C_6H_4OCH_2CO_2\}$, 75
$CuC_{15}H_{12}N_3O_2$
$Cu\{1\text{-}(2\text{-}pyN{=}N)\text{-}2\text{-}OC_{10}H_6\}(H_2O)$, 74
$CuC_{15}H_{16}N_4O$

Cu{2-(2-O-5-MeC$_6$H$_3$N=N)C$_6$H$_4$NCH$_2$CH$_2$NH$_2$}, 76
CuC$_{15}$H$_{20}$N$_4$O$_2$
[Cu{(2-pyCH$_2$)$_2$NH}(H$_2$NCH$_2$CO$_2$Me)]$^{2+}$, 419
CuC$_{16}$H$_{11}$N$_3$O
Cu{1-(2-OC$_6$H$_4$N=N)-2-HNC$_{10}$H$_6$}, 58
CuC$_{16}$H$_{11}$N$_5$O$_5$
Cu{2-{2-O$_2$CC$_6$H$_4$N=NC(CN)=NN}-C$_6$H$_4$CO$_2$H}(H$_2$O), 82
CuC$_{16}$H$_{12}$N$_2$O$_3$
Cu{1-(2-OC$_6$H$_4$N=N)-2-OC$_{10}$H$_6$}(H$_2$O), 55
CuC$_{16}$H$_{14}$N$_2$O$_2$
Cu{(2-OC$_6$H$_4$CH=NCH$_2$)$_2$}, 85
CuC$_{16}$H$_{18}$N$_2$O$_4$
[Cu(2-pyCO$_2$Et)]$^{2+}$, 469
CuC$_{16}$H$_{32}$N$_4$
[Cu{N=CMeCH$_2$CMe$_2$NHCH$_2$CH$_2$N=CMeCH$_2$CMe$_2$NHCH$_2$CH$_2$}]$^{2+}$, 164
CuC$_{16}$H$_{34}$N$_4$O
[Cu{H$_2$NCH$_2$CH$_2$NHCMe$_2$CH$_2$C(Me)=NCH$_2$CH$_2$NHCMe$_2$CH$_2$COMe}]$^{2+}$, 164
CuC$_{17}$H$_{13}$ClN$_2$O$_2$
Cu{1-(2-MeOC$_6$H$_4$N=N)-2-OC$_{10}$H$_6$}Cl, 54
CuC$_{18}$H$_{12}$N$_2$O$_2$
Cu(8-quinolinolate), 1023
CuC$_{18}$H$_{12}$N$_2$O$_{14}$S$_4$
Cu{5,7-(HO$_3$S)$_2$-8-quinolinolate}$_2$, 760
CuC$_{18}$H$_{18}$N$_4$O$_2$
[Cu(terpy)(H$_2$NCH$_2$CO$_2$Me)]$^{2+}$, 419
CuC$_{19}$H$_9$Cl$_2$N$_6$O$_{12}$S$_3$
[Cu{1-O-2-(2-O-5-O$_3$SC$_6$H$_3$N=N)-3, 5-(O$_3$S)$_2$-6-{C=NC(Cl)=NC(Cl)=NNH}C$_{10}$H$_3$}(H$_2$O)]$^{3-}$, 46
CuC$_{19}$H$_{14}$N$_4$O
Cu{2-OC$_6$H$_4$N=NC(Ph)=NNPh}, 79
CuC$_{20}$H$_{14}$N$_4$O$_2$
Cu{2-O$_2$CC$_6$H$_4$N=NC(Ph)=NNPh}, 79
CuC$_{20}$H$_{14}$N$_4$O$_3$
Cu{2-{2-HOC$_6$H$_4$N=NC(Ph)=NN}C$_6$H$_4$CO$_2$}, 82
CuC$_{20}$H$_{16}$ClN$_4$O$_2$
Cu{2-HO$_2$CC$_6$H$_4$N=NC(Ph)=NNHPh}Cl, 79
CuC$_{20}$H$_{16}$N$_4$
[Cu(bipy)$_2$]$^{2+}$, 113
CuC$_{21}$H$_{14}$Cl$_2$N$_5$O$_4$S
[Cu{2-{2-O-5-ClC$_6$H$_3$NCH=C(N=NC$_6$H$_4$SO$_2$NH$_2$)-CH=N}-4-ClC$_6$H$_3$O}]$^-$, 83
CuC$_{21}$H$_{15}$N$_3$O$_2$
Cu{1-(2-OC$_6$H$_4$N=N)-2-OC$_{10}$H$_6$}(py), 55
CuC$_{21}$H$_{18}$ClN$_3$O$_4$
Cu{1-(2-O-5-ClC$_6$H$_3$N=N)-2-O-3-{MeO(CH$_2$)$_3$NHCO}C$_{10}$H$_5$}, 105
CuC$_{22}$H$_{18}$N$_6$
Cu(2-pyNN=NPh)$_2$, 1023
CuC$_{23}$H$_{21}$N$_4$
[Cu(NCH=CPhCH=NCH=CHCH=NCH=CPhCH=NCH$_2$CH$_2$)]$^+$, 168
CuC$_{24}$H$_{16}$N$_4$
[Cu(phen)$_2$]$^+$, 26
[Cu(phen)$_2$]$^{2+}$, 26
CuC$_{24}$H$_{18}$N$_4$O$_2$
Cu(2-OC$_6$H$_4$N=NPh)$_2$, 43
CuC$_{24}$H$_{18}$N$_4$S$_2$
Cu{2-(2-pyCH=N)C$_6$H$_4$S}$_2$, 157
CuC$_{25}$H$_{16}$N$_4$O
Cu{1-{2-(8-quinolinamino)C$_6$H$_4$N=N}-2-OC$_{10}$H$_6$}, 76
CuC$_{26}$H$_{20}$N$_2$O$_2$
Cu(2-OC$_6$H$_4$CH=NPh)$_2$, 43, 157
Cu(2-OC$_6$H$_4$N=CHPh)$_2$, 43
CuC$_{28}$H$_{14}$O$_6$
Cu(anthraquinon-1-olate)$_2$, 86
CuC$_{30}$H$_{32}$N$_4$
Cu(Me$_6$Et$_2$porphyrin), 197
CuC$_{32}$H$_{16}$N$_8$
Cu(phthalocyanine), 39, 87, 89, 123, 1023
CuC$_{32}$H$_{20}$Cl$_2$N$_4$O$_2$
Cu{1-(2-ClC$_6$H$_4$N=N)-2-OC$_{10}$H$_6$}$_2$, 56
CuC$_{32}$H$_{22}$N$_4$O$_2$
Cu{1-(PhN=N)-2-OC$_{10}$H$_6$}$_2$, 42, 43
CuC$_{32}$H$_{24}$N$_6$
Cu{1-(PhN=N)-2-HNC$_{10}$H$_6$}$_2$, 44
CuC$_{32}$H$_{36}$N$_4$
Cu(Me$_4$Et$_4$porphyrin), 197
CuC$_{34}$H$_{20}$Cl$_2$N$_4$O$_2$S$_2$
Cu{1-(5-chloro-2-benzothiazolyl-N=CH)-2-O-C$_{10}$H$_6$}, 1023
CuC$_{34}$H$_{26}$N$_4$O$_4$
Cu{1-(2-MeOC$_6$H$_4$N=N)-2-OC$_{10}$H$_6$}$_2$, 54
CuC$_{36}$H$_{43}$N$_3$O$_{16}$S$_4$
Cu{1-{1-O-4,8-(HO$_3$S)$_2$-6-(C$_{15}$H$_{31}$CONH)-2-C$_{10}$H$_3$N=N}-2-O-3,6-(HO$_3$S)$_2$-8-HOC$_{10}$H$_3$}, 105
CuC$_{36}$H$_{44}$N$_4$
Cu(octaethylporphyrin), 147
CuC$_{36}$H$_{70}$O$_4$
Cu{O$_2$C(CH$_2$)$_{16}$Me}$_2$, 121
CuC$_{38}$H$_{30}$N$_8$
Cu(NPhN=CPhN=NPh)$_2$, 78
CuC$_{38}$H$_{31}$N$_8$
Cu(NPhN=CPhN=NPh)(NHPhN=CPhN=NPh), 78
CuC$_{41}$H$_{24}$N$_6$O$_{31}$S$_8$
Cu{4,8-(HO$_3$S)$_2$-5-O-6-{2-O-3,6-(HO$_3$S)$_2$-8-HOC$_{10}$H$_3$N=N}C$_{10}$H$_3$-2-NH}$_2$CO, 105
CuC$_{41}$H$_{25}$N$_{11}$O
Cu(dehydrophthalocyanine)(1,3-diiminoisoindoleno)-(OMe), 90
CuC$_{54}$H$_{45}$BrP$_3$
CuBr(PPh$_3$)$_3$, 250
CuC$_{68}$H$_{60}$N$_{12}$O$_{16}$S$_4$
Cu{{2,5-(HO)$_2$C$_6$H$_3$CH$_2$CHMeNHSO$_2$}$_4$-phthalocyanine}, 107
CuCl$_2$
[CuCl$_2$]$^-$, 497, 851
CuCl$_3$
[CuCl$_3$]$^{2-}$, 496, 497, 853
CuCl$_4$
[CuCl$_4$]$^{2-}$, 847, 854
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PbCuFe$_2$(SO$_4$)$_2$(OH)$_6$, 827
CuH$_3$S$_3$
[Cu(HS)$_3$]$^-$, 853
CuH$_3$S$_4$
[CuS(HS)$_3$]$^{3-}$, 853
CuH$_4$S$_4$
[Cu(HS)$_4$]$^{2-}$, 853
CuMnC$_{16}$H$_{16}$N$_3$O$_6$
Cu{O$_2$CCH$_2$NCOCH$_2$N=CHC$_5$H$_3${Mn(CO)$_3$}-CH$_2$NMe$_2$}, 209
CuMnC$_{18}$H$_{20}$N$_3$O$_6$
Cu{O$_2$CCHMeNCOCHMeN=CHC$_5$H$_3$-{Mn(CO)$_3$}CH$_2$NMe$_2$}, 209
CuNaC$_{16}$H$_{11}$N$_2$O$_6$S
Cu{1-(2-O-5-NaO$_3$SC$_6$H$_3$N=N)-2-OC$_{10}$H$_6$}(H$_2$O), 56
CuO$_{14}$P$_4$
[Cu(P$_2$O$_7$)$_2$]$^{6-}$, 10
Cu$_2$C$_2$H$_6$O$_6$
{Cu$_2$(OH)$_2$(OOH)(OAc)}$_n$, 330
Cu$_2$C$_6$H$_2$N$_6$
Cu$_2$H$_2$(CN)$_4$(C$_2$N$_2$), 872
Cu$_2$C$_8$H$_{16}$O$_{10}$
Cu$_2$(OAc)$_4$(H$_2$O)$_2$, 1022
Cu$_2$C$_{12}$H$_{16}$Cl$_2$N$_2$O$_2$
Cu$_2$(μ-OMe)$_2$Cl$_2$(py)$_2$, 389
Cu$_2$C$_{12}$H$_{20}$O$_6$
Cu$_2$(OMe)$_2$(acac)$_2$, 470
Cu$_2$C$_{13}$H$_{11}$ClN$_2$O$_5$
Cu$_2${3,5-(O$_2$CCH$_2$N=CH)$_2$-4-OC$_6$H$_2$Me}Cl, 158
Cu$_2$C$_{19}$H$_{23}$N$_4$O$_2$

$[Cu_2\{4,5\text{-}(2\text{-}pyCH_2CH_2N{=}CH)_2imidazole\}(H_2O)_2]^{3+}$, 158

$Cu_2C_{20}H_{37}N_4O_3$
$[Cu_2(Me_2NCH_2CH_2NMe_2)_2(\mu\text{-}CO)(\mu\text{-}O_2CPh)]^+$, 395

$Cu_2C_{21}H_{15}ClN_2O_3$
$Cu_2\{3,5\text{-}(2\text{-}OC_6H_4N{=}CH)_2\text{-}4\text{-}OC_6H_2Me\}Cl$, 158

$Cu_2C_{24}H_{48}O_4$
$Cu_2\{O(CH_2)_3NHCMe_2CH_2C(Me){=}N(CH_2)_3O\}_2$, 164

$Cu_2C_{36}H_{32}Br_2P_2$
$Cu_2H_2Br_2(PPh_3)_2$, 250

$Cu_2C_{38}H_{28}N_8O_2$
$Cu_2\{2\text{-}OC_6H_4N{=}NC(Ph){=}NNPh\}_2$, 80

$Cu_2C_{38}H_{32}N_6O_6$
$Cu_2\{\{2\text{-}\{2\text{-}OC_6H_4N{=}C(CON\overline{(CH_2)_4})\}C_6H_4NCO\}_2\}$, 179

$Cu_2C_{40}H_{28}N_4O_4$
$Cu_2\{2\text{-}O_2CC_6H_4N{=}NC(Ph){=}NNPh\}_2$, 80

$Cu_2C_{84}H_{70}Br_2N_2P_4$
$Cu_2Br_2(PPh_3)_4(PhN{=}NPh)$, 250

Cu_2O_5S
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$Cu_4C_6H_9Cl_4N_3O_2$
$Cu_4Cl_4O_2(MeCN)_3$, 392

$Cu_4C_{15}H_{15}Cl_4N_3O_2$
$Cu_4(\mu_2\text{-}O)Cl_4(py)_3$, 389, 393

$Cu_4C_{20}H_{20}Cl_4N_4O_2$
$Cu_4Cl_4O_2(py)_4$, 394

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$Cu_{40}H_{28}N_8O_{14}S_2$
$Cu\{\{2\text{-}MeO\text{-}4\text{-}(2\text{-}O\text{-}5\text{-}HO_3SC_6H_3N{=}N)\text{-}5\text{-}OC_6H_2N{=}N(O)\}C_6H_4CH{=}\}_2$, 106

$FeAsH_{13}N_3O_2$
$Fe\{As(O)(OH)Me\}(NH_3)_3$, 1018

$FeC_2N_2S_2$
$[Fe(SCN)_2]^+$, 823

$FeC_4H_4O_{10}$
$[Fe(C_2O_4)_2(H_2O)_2]^-$, 125

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$FeC_5H_2N_5O$
$[Fe(CN)_5(H_2O)]^{3-}$, 18

$FeC_6H_9O_6$
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$[Fe(CN)_6]^{2-}$, 494, 873, 1017
$[Fe(CN)_6]^{3-}$, 16, 17, 22, 100, 124, 494, 529, 530, 621, 652, 822, 830, 1017
$[Fe(CN)_6]^{4-}$, 17, 22, 24, 30, 124, 496, 652, 822, 847

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$[Fe(C_2O_4)_3]^{3-}$, 114, 117, 125, 849, 1017

$FeC_9H_{18}N_3S_6$
$Fe(S_2CNMe_2)_3$, 1017

$FeC_{10}H_{10}$
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$FeC_{10}H_{12}N_2O_8$
$[Fe(edta)]^-$, 25, 100, 652
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$FeC_{11}H_{10}O$
$FeCp(C_5H_4CHO)$, 20

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$FeCp(H_2C{=}CHC_5H_4)$, 16, 19

$FeC_{15}H_{21}O_6$
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$FeC_{16}H_{16}S_4$
$[Fe\{1,2\text{-}(SCH_2)_2C_6H_4\}_2]^{2-}$, 627

$FeC_{16}H_{28}N_4$
$[Fe(\overline{N{=}CHCH{=}NCMe_2CH_2CHMeN{=}CHCH{=}NCMe_2CH_2CHMe})]^{2+}$, 165

$FeC_{16}H_{32}N_4$
$[Fe(\overline{N{=}CMeCH_2CMe_2NHCH_2CH_2N{=}CMeCH_2\text{-}CMe_2NHCH_2CH_2})]^{2+}$, 165

$FeC_{20}H_{21}N_4O_2$
$Fe(OAc)(\overline{N{=}CHC_6H_4NCH_2CH_2NC_6H_4CH{=}N\text{-}CH_2CH_2})$, 176

$FeC_{21}H_{12}N_9O_6$
$[Fe(7\text{-}nitroso\text{-}6\text{-}indazololate)_3]^-$, 85

$FeC_{21}H_{18}N_3O_6$
$Fe(2\text{-}OC_6H_4CH{=}NOH)_3$, 800

$FeC_{23}H_{24}N_6$
$[Fe\{(2\text{-}pyCH{=}NCH_2)_3CMe\}]^{2+}$, 158

$FeC_{24}H_{20}S_4$
$[Fe(SPh)_4]^-$, 627
$[Fe(SPh)_4]^{2-}$, 627

$FeC_{27}H_{27}N_9O_6$
$[Fe(1,2\text{-}dimethyl\text{-}7\text{-}nitroso\text{-}6\text{-}indazololate)_3]^{2+}$, 85

$FeC_{30}H_{15}N_3O_{15}S_3$
$[Fe(1\text{-}ON\text{-}2\text{-}O\text{-}6\text{-}O_3SC_{10}H_5)_3]^{4-}$, 85

$FeC_{30}H_{24}N_6$
$[Fe(bipy)_3]^{2+}$, 23, 494, 520
$[Fe(bipy)_3]^{3+}$, 494, 516, 519, 523

$FeC_{32}H_{16}N_8$
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$FeC_{34}H_{34}N_4O_4$
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$FeC_{36}H_{16}N_8$
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$FeC_{36}H_{24}N_6$
$[Fe(phen)_3]^{2+}$, 26
$(Fe(phen)_3]^{3+}$, 516

$FeC_{36}H_{46}N_4$
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$FeC_{38}H_{32}O_2P_2$
$FeH_2(CO)_2(PPh_3)_2$, 231

$FeC_{39}H_{30}O_3P_2$
$Fe(CO)_3(PPh_3)_2$, 258

$FeC_{44}H_8ClF_{20}N_4$
FeCl{tetrakis(pentafluorophenyl)porphyrin}, 382

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$[Fe(tetraphenylporphyrin)Cl]^+$, 618

$FeC_{44}H_{28}N_4$
Fe(tetraphenylporphyrin), 614

$FeC_{44}H_{28}N_4O_2$
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$[Fe(tetraphenylporphyrin)(H_2O)_2]^+$, 618

$FeC_{46}H_{28}N_6$
$[Fe(tetraphenylporphyrin)(CN)_2]^-$, 618

$FeC_{48}H_{28}N_7$
$[Fe(tetraphenylporphyrin)\{C(CN)_3\}]_n$, 618

$FeC_{48}H_{34}N_6O$
FeO(tetraphenylporphyrin)(Me$\overline{NCH{=}NCH{=}CH}$), 383

$FeC_{48}H_{40}N_4O_2S_2$
$[Fe(tetraphenylporphyrin)(DMSO)_2]^+$, 618

$FeC_{52}H_{44}N_4O_2$
$Fe(tetraphenylporphyrin)(THF)_2$, 618

$FeC_{68}H_{70}N_{10}O_6$
$Fe\{\alpha,\alpha,\alpha,\alpha\text{-}(2\text{-}Bu^tCONHC_6H_4)_4porphyrin\}\text{-}(MeNHCH{=}NCH{=}CH)(O_2)$, 320, 685

$FeCl_4$
$[FeCl_4]^-$, 802, 803, 808, 814

$FeCrH_3O_3$
$[Fe(OH)(OH)_2Cr]^{3+}$, 852

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$[Fe(OH)(OH)_2Cr(OH)]^{2+}$, 852

$FeCrH_5O_5$
$[Fe(OH)_2(OH)_2Cr(OH)]^+$, 852

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$[Fe(H_2O)_6]^{3+}$, 494, 808
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$[Mo(S_2)_2Fe(SPh)_2]^{2-}$, 722
$FeMo_2S_8$
$[Mo(S_2)_2Fe(S_2)Mo(S_2)]^{3-}$, 722
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$Fe_2C_{36}H_{24}N_8O_5$
$\{Fe(N{=}CHC_6H_4NCOCONC_6H_4CH{=}NCH_2CH_2)\}_2O$, 176
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$Fe_3C_{24}H_{20}S_8$
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$[Fe_3S\{1,2\text{-}(SCH_2)_2C_6H_4\}_3]^{2-}$, 633
$Fe_3C_{27}H_{33}N_3O_{13}$
$Fe_3O(OAc)_6(py)_3$, 384
$Fe_3C_{30}H_{36}S_7$
$[Fe_3S\{1,2\text{-}SCH_2\}_2\text{-}4,5\text{-}Me_2C_6H_2\}_3]^{2-}$, 633
$Fe_3C_{33}H_{66}O_{16}$
$[Fe_3O(O_2CBu^t)_6(MeOH)_3]^+$, 384
$Fe_3H_6O_{14}S_2$
$[Fe_3(SO_4)_2(OH)_6]^-$, 827
$Fe_4C_8H_{20}O_4S_8$
$[Fe_4S_4(SCH_2CH_2OH)_4]^{2-}$, 630
$Fe_4C_{12}H_{24}N_4O_8S_8$
$[Fe_4S_4\{SCH_2CH(NH_2)CO_2H\}_4]^-$, 629
$[Fe_4S_4\{SCH_2CH(NH_2)CO_2H\}_4]^{2-}$, 629
$[Fe_4S_4\{SCH_2CH(NH_2)CO_2H\}_4]^{3-}$, 629
$Fe_4C_{16}H_{36}S_8$
$[Fe_4S_4(SBu^t)_4]^{2-}$, 630
$Fe_4C_{24}H_{20}S_8$
$[Fe_4S_4(SPh)_4]^{2-}$, 630
$Fe_4C_{24}H_{44}N_8O_{12}S_8$
$Fe_4S_4\{SCH_2CH(NHAc)CO_2NHMe\}_4]^{2-}$, 630
$Fe_4C_{28}H_{28}S_8$
$[Fe_4S_4(SCH_2Ph)_4]^{2-}$, 508
$[Fe_4S_4(SCH_2Ph)_4]^{n-}$, 630
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$GaCl_4$
$[GaCl_4]^{2-}$, 854
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$HgC_2N_2O_2$
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$HgC_6H_{12}O_6S_4$
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$HgC_8H_8O_2$
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$Hg\{CH_2CH(Ph)OOH\}(O_2CCF_3)$, 340
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$[Ir(CO)_2Cl_2]^-$, 136, 142
$IrC_2H_{18}N_6$
$[Ir(NH_3)_5(NCMe)]^{3+}$, 449
$IrC_2I_2O_2$
$[IrI_2(CO)_2]^-$, 278
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$Ir(CO)_3Br$, 151

IrC_3ClO_3
$Ir(CO)_3Cl$, 151
$IrC_3H_{22}N_6O$
$[Ir(NH_3)_5(DMF)]^{3+}$, 433
IrC_3IO_3
$Ir(CO)_3I$, 151
$IrC_3I_3O_3$
$IrI_3(CO)_3$, 278
$IrC_8H_{13}Cl_2$
$IrHCl_2(C_8H_{12})$, 350
$IrC_{16}H_{28}Cl_2$
$IrCl(C_8H_{14})_2$, 246
$IrC_{22}H_{38}NP$
$[Ir(cod)(py)(PPr^i_3)]^+$, 246
$IrC_{26}H_{24}O_2P_2$
$[Ir(O_2)(dppe)]^+$, 329
$IrC_{29}H_{30}ClO_3P_2$
$Ir(O_2)Cl(CO)(PPh_2Et)_2$, 321
$IrC_{30}H_{45}Cl_3P_3$
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$IrC_{31}H_{50}NP$
$[Ir(cod)(py)\{P(C_6H_{11})_3\}]^+$, 246
$IrC_{32}H_{44}O_2P_4$
$[Ir(O_2)(PMe_2Ph)_4]^+$, 329
$IrC_{32}H_{48}$
$[Ir(C_8H_{12})_4]^+$, 350
$IrC_{32}H_{56}$
$[Ir(C_8H_{14})_4]^+$, 341
$IrC_{34}H_{38}P_2$
$[Ir(cod)(PMePh_2)_2]^+$, 246
$IrC_{36}H_{81}Cl_3P_3$
$IrCl_3(PBu_3)_3$, 303
$IrC_{37}H_{30}ClOP_2$
$IrCl(CO)(PPh_3)_2$, 247, 263, 303, 1019
$IrC_{37}H_{30}ClO_3P_2$
$IrCl(CO)(O_2)(PPh_3)_2$, 1019
$IrC_{37}H_{30}IO_3P_2$
$Ir(O_2)I(CO)(PPh_3)_2$, 329
$IrC_{37}H_{66}ClOP_2$
$IrCl(CO)\{P(C_6H_{11})_3\}_2$, 247
$IrC_{38}H_{31}O_2P_2$
$IrH(CO)_2(PPh_3)_2$, 303
$IrC_{38}H_{34}ClO_2P_2$
$Ir(O_2)Cl(H_2C{=}CH_2)(PPh_3)_2$, 341
$IrC_{42}H_{44}O_2P_2$
$[IrH_2(OCMe_2)_2(PPh_3)_2]^+$, 246
$IrC_{45}H_{48}ClO_3P_2$
$IrCl(OOBu^t)_2(CO)(PPh_3)_2$, 330
$IrC_{53}H_{51}P_4S_2$
$[Ir(\eta^2\text{-}S_2Me)(dppe)_2]^{2+}$, 350
$IrC_{54}H_{45}ClP_3$
$IrCl(PPh_3)_3$, 246
$IrC_{54}H_{47}ClP_3$
$IrH_2Cl(PPh_3)_3$, 303
$IrC_{54}H_{48}P_3$
$IrH_3(PPh_3)_3$, 246, 294
$IrC_{55}H_{46}OP_3$
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$[Ir(NH_3)_5(OH)]^{2-}$, 435
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$Ir_2H_5(PPh_3)_4$, 246

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$[LnF_6]^{3-}$, 846
LnO_8S_2
$[Ln(SO_4)_2]^{2+}$, 854
$LuC_8H_{11}NO_6$
$[Lu\{EtO_2CCH_2N(CH_2CO_2)_2\}]^+$, 422

$MgC_3H_6O_4$
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$MgC_7H_{13}BrO$
$MgBr\{OC(Bu^t){=}CHMe\}$, 218
$MgC_{18}H_{12}N_2O_2$
$Mg(8\text{-quinolinolate})_2$, 123
$MgC_{55}H_{70}N_4O_6$
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$MgC_{55}H_{72}N_4O_5$
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$MnC_4H_2O_5$
$Mn(O_2CCOCH_2CO_2)$, 455
$MnC_4H_6N_2S_4$
$Mn(S_2CNHCH_2CH_2NHCS_2)$, 1016
$MnC_{10}H_{14}O_4$
$Mn(acac)_2$, 280, 1016
$MnC_{10}H_{14}O_6$
$MnO_2(acac)_2$, 121
$MnC_{12}H_{22}O_{14}$
$Mn\{O_2C(CHOH)_4CH_2OH\}_2$, 534
$MnC_{15}H_{21}O_6$
$Mn(acac)_3$, 1016
$MnC_{16}H_{14}N_2O_2$
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$MnC_{32}H_{16}N_8$
Mn(phthalocyanine), 1016
$MnC_{44}H_{28}ClN_4$
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$MnC_{44}H_{28}N_7$
$Mn(N_3)$(tetraphenylporphyrin), 377
$MnC_{46}H_{31}N_4O_2$
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$MnC_{60}H_{46}I_2N_4O_6$
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$MnCuC_{16}H_{16}N_3O_6$
$Cu\{O_2CCH_2NCOCH_2N{=}CHC_5H_3\{Mn(CO)_3\}\text{-}CH_2NMe_2\}$, 209
$MnCuC_{18}H_{20}N_3O_6$
$Cu\{O_2CCHMeNCOCHMeN{=}CHC_5H_3\{Mn(CO)_3\}\text{-}CH_2NMe_2\}$, 209
$MnH_{12}O_6$
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$[MnP_2O_7]^-$, 125
$Mn_2C_{34}H_{36}N_4O_6$
$\{Mn\{(2\text{-}OC_6H_4CH{=}NCH_2)_2CH_2\}(H_2O)\}_2$, 498
$Mn_2C_{40}H_{32}N_8O_2$
$[Mn_2O_2(bipy)_4]^{3+}$, 498
$[Mn_2O_2(bipy)_4]^{4+}$, 498
$Mn_2C_{88}H_{58}N_{14}O$
$\{Mn(tetraphenylporphyrin)(N_3)\}_2O$, 378
$Mn_2C_{100}H_{66}Cl_2I_2N_8O_3$
$\{Mn(tetraphenylporphyrin)\{OI(Ph)Cl\}\}_2O$, 378
$MoC_5H_{11}NO_7$
$MoO(O_2)_2\{Me_2NCOCH(OH)Me\}$, 329
$MoC_6H_4NO_7$
$[MoO(O_2)_2(2\text{-}pyCO_2)]^-$, 332
$MoC_6H_{14}Cl_2N_2O_4$
$MoO_2Cl_2(DMF)_2$, 351
$MoC_6H_{20}N_3O_7P$
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$MoC_7H_3NO_7$
$MoO(O_2)\{2,6\text{-}py(CO_2)_2\}$, 331
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$MoO_2(S_2CNEt_2)_2$, 351, 354
$MoC_{11}H_{23}N_4O_6P$
$MoO(O_2)_2(py)(HMPA)$, 331
$MoC_{12}H_{21}ClN_4O_6P$
$MoO(O_2)Cl(2\text{-}pyCO_2)(HMPA)$, 329
$MoC_{21}H_{18}S_6$
$Mo(3,4\text{-}S_2C_6H_3Me)_3$, 1015
$MoC_{26}H_{20}N_2O_7$
$MoO(O_2)(ONPhCOPh)_2$, 331
$MoC_{28}H_{24}O_2S_8$
$MoO_2\{2\text{-}(2\text{-}SC_6H_4SCH_2CH_2S)C_6H_4S\}_2$, 658
$MoC_{35}H_{30}S_{10}$
$Mo_2(3,4\text{-}S_2C_6H_3Me)_5$, 1015
$MoC_{41}H_{39}Br_3P_3$
$MoBr_3$(triphos), 719
$MoC_{44}H_{28}N_4O_4$
$Mo(O_2)_2$(tetraphenylporphyrin), 329
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$\{Mo(S_2)_2Fe(SPh)_2\}^{2-}$, 722
$MoHO_7$
$[MoO(O_2)_2OOH]^-$, 330
MoH_6O_6
$Mo(OH)_6$, 944
MoO_4
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MoS_4
$[MoS_4]^{2-}$, 657, 805, 828
Mo_2Br_8
$[Mo_2Br_8]^{4-}$, 496
$Mo_2C_{88}H_{56}N_8O_3$
Mo_2O_3(tetraphenylporphyrin)$_2$, 616
Mo_2FeS_8
$[Mo(S_2)_2Fe(S_2)Mo(S_2)]^{3-}$, 722
Mo_2HCl_8
$[Mo_2Cl_8H]^{3-}$, 496
$Mo_2H_{2n}O_n$
$[Mo_2(H_2O)_n]^{4+}$, 496
Mo_2O_7
$[Mo_2O_7]^-$, 806
$[Mo_2O_7]^{2-}$, 1015
$Mo_2O_{16}S_4$
$[Mo_2(SO_4)_4]^{4-}$, 496
$Mo_3C_6H_{12}S_{10}$
$[Mo_3S_4(SCH_2CH_2S)_3]^{2-}$, 633
Mo_4O_{13}
$[Mo_4O_{13}]^{2-}$, 806
Mo_8O_{26}
$[Mo_8O_{26}]^{4-}$, 806
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$[Nb(O_2)_2(C_2O_4)_2]^{3-}$, 329
$NbC_{10}H_{10}ClO_2$
$Nb(O_2)Cp_2Cl$, 321, 329
$NbC_{12}H_8N_2O_8$
$[Nb(O_2)_2(2\text{-}pyCO_2)_2]^-$, 329
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NbF_6
$[NbF_6]^-$, 813
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$Nb(OH)_5$, 944
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Nb_2O_3(tetraphenylporphyrin)$_2$, 616
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$NiB_2C_8H_{12}F_4N_4O_4$
$Ni\{\overline{N{=}CMeC(Me){=}NOBF_2ON{=}CMeC(Me){=}N\text{-}OBF_2O}\}$, 185
$NiB_2C_{32}H_{32}N_4O_4$
$Ni\{\overline{N{=}CMeC(Me){=}NOBPh_2ON{=}CMeC(Me){=}N\text{-}OBPh_2O}\}$, 185
NiC_3IO_3
$[NiI(CO)_3]^-$, 279
$NiC_4H_2O_5$
$Ni(O_2CCOCH_2CO_2)$, 455
$NiC_4H_6O_4$
$Ni(OAc)_2$, 1019
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$[Ni(en)_2]^{2+}$, 150, 163
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$Ni(CO)_4$, 768
$NiC_6H_4N_2$
$[Ni(2\text{-}pyCN)]^{2+}$, 453
$NiC_6H_{20}Cl_3N_4$
$Ni(pn)_2Cl_3$, 150
$NiC_6H_{24}N_6$
$[Ni(en)_3]^{2+}$, 163, 164
$NiC_8H_4N_8$
$Ni\{(HN)_2C_2(CN)_2\}_2$, 112
$NiC_8H_5NO_3$
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$NiC_8H_{10}N_8O_{10}$
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$NiC_8H_{11}NO_6$
$Ni\{EtO_2CCH_2N(CH_2CO_2)_2\}$, 422
$NiC_8H_{14}N_4O_4$
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$NiC_8N_4S_4$
$[Ni\{S_2C_2(CN)_2\}_2]^-$, 147
$[Ni\{S_2C_2(CN)_2\}_2]^{2-}$, 147
$NiC_9H_{13}N_2O_8$
$[Ni\{N(CH_2CO_2)_3\}(H_2NCH_2CO_2Me)]^-$, 418
$NiC_9H_{17}N_3O_6$
$Ni\{H_2NCH_2CH_2N(CH_2CO_2)_2\}(H_2NCH_2CO_2Me)$, 418
$NiC_9H_{25}N_5O_2$
$[Ni\{(H_2NCH_2CH_2NHCH_2)_2\}(H_2NCH_2CO_2Me)]^{2+}$, 418
$[Ni\{N(CH_2CH_2NH_2)_3\}(H_2NCH_2CO_2Me)]^{2+}$, 418
$NiC_9H_{30}N_6$
$[Ni(pn)_3]^{2+}$, 165
$NiC_{10}H_5N_2O$
$[Ni(2\text{-cyano-8-quinolinolate})]^+$, 453
$NiC_{10}H_{12}N_6$
$[Ni\{3,3'\text{-}(H_2NNH)_2bipy\}]^{2+}$, 184
$NiC_{10}H_{14}N_8$
$Ni\{\overline{N{=}CMeC(Me){=}NNCH{=}NN{=}CMeC(Me){=}N\text{-}NCH{=}N}\}$, 182
$[Ni\{\overline{N{=}CMeC(Me){=}NNCH{=}NN{=}CMeC(Me){=}NNCH{=}N}\}]^+$, 182
$NiC_{10}H_{14}O_2S_2$
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$NiC_{10}H_{14}O_4$
$Ni(acac)_2$, 205, 248
$NiC_{10}H_{18}N_2O_2$
$Ni(O_2)(CNBu^t)_2$, 321, 329
$NiC_{10}H_{20}N_2S_4$
$Ni(S_2CNEt_2)_2$, 1021
$NiC_{10}H_{20}N_8$
$[Ni\{\overline{N{=}CMeC(Me){=}NNHCH_2NHN{=}CMeC(Me){=}NNHCH_2NH}\}]^{2+}$, 182
$NiC_{11}H_{15}N_7$
$[Ni\{\overline{N{=}CMeC(Me){=}NCH{=}CHNN{=}CMeC(Me){=}NN{=}CHN}\}]^{2+}$, 182
$NiC_{11}H_{24}N_4$
$[Ni(\overline{N{=}CHCMe_2CH_2NHCH_2CH_2NHCH_2\text{-}CH_2NHCH_2CH_2}\,)]^{2+}$, 164
$NiC_{12}H_{10}I_{0.52}N_4O_4$
Ni(benzoquinone dioxime)$_2I_{0.52}$, 144
$NiC_{12}H_{10}N_2O_4S_4$
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$RhH(CO)(3\text{-}HO_3SC_6H_4PPh_2)_3$, 263

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$RhH(CO)(PPh_3)_3$, 265

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$Rh_2(CO)_4\{N(CH_2Ph)_3\}_2$, 263

$Rh_2C_{52}H_{44}ClO_2P_4$
$[Rh_2Cl(CO)_2(dppm)_2]^+$, 244

$Rh_2C_{56}H_{44}N_2O_4P_4$
$Rh_2(CN)_2(CO)_4(dppm)_2$, 244

$Rh_2C_{72}H_{60}Cl_2O_4P_4$
$Rh_2(O_2)_2Cl_2(PPh_3)_4$, 322

$Rh_2C_{72}H_{132}N_2P_4$
$Rh_2(N_2)\{P(C_6H_{11})_3\}_4$, 242

Rh_2Cl_9
$[Rh_2Cl_9]^{3-}$, 809

$Rh_4C_{12}O_{12}$
$Rh_4(CO)_{12}$, 262, 265

$Rh_4C_{40}H_{48}Br_2N_6$
$[Rh_4\{CN(CH_2)_3NC\}_8Br_2]^{4+}$, 496

$Rh_4C_{40}H_{48}Cl_2N_{16}$
$[Rh_4\{CN(CH_2)_3NC\}_8Cl_2]^{4+}$, 496

$Rh_6C_{16}O_{16}$
$Rh_6(CO)_{16}$, 274

$RuAsC_{47}H_{39}F_3O_3P_2$
$Ru(O_2CCF_3)(CO)(PPh_3)(arphos)$, 235

$RuCH_{19}N_7O$
$[Ru(NH_3)_5(H_2NCONH_2)]^{3+}$, 471

$RuC_2H_{18}N_6$
$[Ru(NH_3)_5(NCMe)]^{2+}$, 449, 450, 458, 496
$[Ru(NH_3)_5(NCMe)]^{3+}$, 449, 450, 452

$RuC_3I_3O_3$
$[RuI_3(CO)_3]^-$, 267

$RuC_4H_{18}N_6$
$[Ru(NH_3)_4\{N{=}C(Me)C(Me){=}N\}]^{2+}$, 458

$RuC_4H_{20}N_6$
$[Ru(NH_3)_4\{HN{=}CMeC(Me){=}NH\}]^{2+}$, 190

$RuC_4I_2O_4$
$RuI_2(CO)_4$, 267
$RuC_5H_{20}N_6$
$[Ru(NH_3)_5(py)]^{2+}$, 652
$[Ru(NH_3)_5(py)]^{3+}$, 652
$RuC_6H_6O_6$
$\{Ru(OAc)_2(CO)_2\}_n$, 268
$RuC_6H_{24}N_6$
$[Ru(en)_3]^{3+}$, 652
RuC_6N_6
$[Ru(CN)_6]^{3-}$, 534
$RuC_7H_{20}N_6$
$[Ru(NH_3)_5(NCPh)]^{2+}$, 458
$[Ru(NH_3)_5(NCPh)]^{3+}$, 449, 450, 452
$RuC_{12}H_{10}Cl_2N_2O_2$
$RuCl_2(CO)_2(py)_2$, 269
$RuC_{15}H_{21}O_6$
$Ru(acac)_3$, 267, 269
$RuC_{19}H_{19}Cl_3OP$
$RuCl_3(PPh_3)(MeOH)$, 258
$RuC_{20}H_{16}Cl_2N_4$
$RuCl_2(bipy)_2$, 17, 499
$RuC_{20}H_{16}N_4$
$[Ru(bipy)_2]^{2+}$, 16
$RuC_{20}H_{16}N_4O$
$[RuO(terpy)(py)]^{2+}$, 18
$RuC_{20}H_{20}Cl_2N_4$
$RuCl_2(py)_4$, 269
$RuC_{20}H_{20}N_4O_2$
$[Ru(bipy)_2(H_2O)_2]^{2+}$, 518
$RuC_{20}H_{49}ClP_2$
$RuHCl(depe)_2$, 303
$RuC_{21}H_{16}ClN_4O$
$[RuCl(CO)(bipy)_2]^{-}$, 269, 499
$RuC_{21}H_{17}N_4O$
$[RuH(CO)(bipy)_2]^{+}$, 499
$RuC_{24}H_{18}N_{12}$
$[Ru(HC{=}NCH{=}CHN{=}CC{=}NCH{=}CHN{=}CH)_3]^{2+}$, 510
$[Ru(N{=}CHCH{=}CHN{=}CC{=}NCH{=}CHCH{=}N)_3]^{2+}$, 510
$RuC_{24}H_{22}N_6$
$[Ru(bipy)_2(MeCN)_2]^{2+}$, 29
$RuC_{24}H_{26}N_4O_2$
$[Ru(bipy)_2(DME)]^{2+}$, 532
$RuC_{24}H_{54}N_4O_{18}P_2$
$Ru(NO)(NO_3)_3\{OP(OBu)_3\}_2$, 942
$RuC_{25}H_{21}ClN_5$
$[Ru(bipy)_2(py)Cl]^{+}$, 30
$RuC_{26}H_{21}ClN_5O_2$
$[Ru(bipy)_2(4\text{-}pyCO_2H)Cl]^{+}$, 20
$RuC_{27}H_{24}N_6$
$[Ru(bipy)_2(py)(MeCN)]^{2+}$, 29
$RuC_{28}H_{22}N_6S$
$[Ru(bipy)_2(2\text{-}pyC{=}NCH{=}CHS)]^{2+}$, 506
$RuC_{28}H_{24}N_8$
$[Ru(bipy)_2(N{=}CHCH{=}NCH{=}CH)_2]^{2+}$, 29
$RuC_{28}H_{32}N_4$
$[Ru(cod)(py)_4]^{2+}$, 269
$RuC_{30}H_{24}N_6$
$[Ru(bipy)_3]^{+}$, 25, 499, 509, 526, 531
$[Ru(bipy)_3]^{2+}$, 15, 16, 23, 25, 26, 29, 31, 400, 498, 499, 500, 501, 502, 505, 506, 507, 508, 509, 510, 513, 515, 517, 519, 520, 521, 524, 525, 526, 527, 528, 529, 530, 531, 552
$[Ru(bipy)_3]^{3+}$, 16, 25, 31, 499, 509, 515, 516, 517, 519, 523, 524, 526, 530, 531
$RuC_{30}H_{26}F_3O_3P_2$
$Ru(O_2CCF_3)(CO)\{Ph_2P(CH_2)_3PPh_2\}$, 235
$RuC_{30}H_{34}ClP$
$RuHCl(\eta^6\text{-}C_6Me_6)(PPh_3)$, 233
$RuC_{31}H_{46}BrOP_3$
$RuHBr(CO)(PEt_2Ph)_3$, 303
$RuC_{33}H_{28}N_6$
$[Ru(bipy)_2(4\text{-}Me\text{-}4'\text{-}H_2C{=}CHbipy)]^{2+}$, 30
$RuC_{34}H_{30}N_6$
$[Ru(bipy)_2(4\text{-}H_2C{=}CHpy)_2]^{2+}$, 30
$RuC_{35}H_{36}P_2$
$[Rh(nbd)(dppb)]^{+}$, 241
$RuC_{36}H_{22}N_6O_4$
$[Ru(bipy)_2\{bipy\text{-}4,4'\text{-}(CO_2Et)_2\}]^{2+}$, 506
$RuC_{36}H_{24}N_6$
$[Ru(phen)_3]^{2+}$, 23, 505, 1018
$RuC_{36}H_{29}ClP_2$
$RuCl(C_6H_4PPh_2)(PPh_3)$, 233
$RuC_{36}H_{30}ClNO_3P_2$
$Ru(O_2)Cl(NO)(PPh_3)_2$, 329
$RuC_{36}H_{30}Cl_2P_2$
$RuCl_2(PPh_3)_2$, 232
$RuC_{36}H_{30}N_2O_2P_2$
$Ru(NO)_2(PPh_3)_2$, 269
$RuC_{36}H_{58}N_4O_4$
$[Ru(bipy)_2\{bipy\text{-}4,4'\text{-}(CO_2NHC_{12}H_{25})_2\}]^{2+}$, 506
$RuC_{38}H_{30}Cl_2O_2P_2$
$RuCl_2(CO)_2(PPh_3)_2$, 232, 234, 235
$RuC_{38}H_{31}ClO_2P_2$
$RuHCl(CO)_2(PPh_3)_2$, 234
$RuC_{38}H_{32}O_2P_2$
$RuH_2(CO)_2(PPh_3)_2$, 258
$RuC_{38}H_{36}N_6O_4$
$[Ru(bipy)_2\{bipy\text{-}4,4'\text{-}(CO_2Pr^i)^2\}]^{2+}$, 531
$RuC_{38}H_{66}Cl_2O_2P_2$
$RuCl_2(CO)_2\{P(C_6H_{11})_3\}_2$, 232
$RuC_{39}H_{30}O_3P_2$
$Ru(CO)_3(PPh_3)_2$, 235, 258, 269
$RuC_{39}H_{36}N_6$
$[Ru(4\text{-}H_2C{=}CH\text{-}4'\text{-}Mebipy)_3]^{2+}$, 19
$RuC_{40}H_{36}O_4P_2$
$Ru(OAc)_2(PPh_3)_2$, 234, 258
$RuC_{41}H_{30}F_6O_5P_2$
$Ru(O_2CCF_3)_2(CO)(PPh_3)_2$, 235
$RuC_{42}H_{36}N_6$
$[Ru(4,7\text{-}Me_2phen)_3]^{2+}$, 506
$RuC_{46}H_{33}O_4P_2$
$Ru(O_2CBu^t)_2(PPh_3)_2$, 258
$RuC_{52}H_{48}P_4$
$[Rh(diphos)_2]^{-}$, 276
$RuC_{54}H_{30}N_6O_6$
$[Ru\{bipy\text{-}4,4'\text{-}(CO_2Pr^i)_2\}_3]^{2+}$, 510
$RuC_{54}H_{45}Cl_2O_9P_3S_3$
$RuCl_2(3\text{-}HO_3SC_6H_4PPh_2)_3$, 234
$RuC_{54}H_{45}Cl_2P_3$
$RuCl_2(PPh_3)_3$, 235, 258, 269, 293, 299, 303, 306, 357
$RuC_{54}H_{46}ClO_9P_3S_3$
$RuHCl(3\text{-}HO_3SC_6H_4PPh_2)_3$, 234
$RuC_{54}H_{46}ClP_3$
$RuHCl(PPh_3)_3$, 232, 233, 235, 303, 304
$RuC_{54}H_{46}NOP_3$
$RuH(NO)(PPh_3)_3$, 235, 258
$RuC_{54}H_{46}P_3$
$[RuH_2(C_6H_4PPh_2)(PPh_3)_2]^{-}$, 233
$RuC_{54}H_{47}P_3$
$RuH_2(PPh_3)_3$, 304
$RuC_{54}H_{48}P_3$
$RuH_4(PPh_3)_3$, 235, 258
$RuC_{55}H_{46}ClOP_3$
$RuHCl(CO)(PPh_3)_3$, 232, 233, 235, 303, 304
$RuC_{55}H_{47}OP_3$
$RuH_2(CO)(PPh_3)_3$, 235, 258, 304
$RuC_{56}H_{48}O_2P_3$
$RuH(OAc)(PPh_3)_3$, 234
$RuC_{56}H_{49}O_{11}P_3S_3$
$RuH(OAc)(3\text{-}HO_3SC_6H_4PPh_2)_3$, 234
$RuC_{56}H_{48}P_3$
$Ru(C_2H_4)(PPh_3)_3$, 304
$RuC_{72}H_{60}Cl_2P_4$

$RuCl_2(PPh_3)_4$, 303
$RuC_{72}H_{62}P_4$
$RuH_2(PPh_3)_4$, 233, 234, 235, 258, 293, 303
$RuCl_5NO$
$[Ru(NO)Cl_5]^{2-}$, 809
$RuCl_6$
$[RuCl_6]^{2-}$, 823
$[RuCl_6]^{3-}$, 298, 823
$RuHN_5O_{10}$
$[Ru(NO)(NO_2)_4(OH)]^{2-}$, 941
RuH_2Cl_5O
$[RuCl_5(H_2O)]^{-}$, 298
$RuH_2N_5O_{14}$
$[Ru(NO)(NO_3)_4(H_2O)]^{-}$, 942
$RuH_4Cl_4O_2$
$[RuCl_4(H_2O)_2]^{-}$, 298
$RuH_4N_4O_{12}$
$Ru(NO)(NO_3)_3(H_2O)_2$, 942
$RuH_{15}N_6O_2$
$[Ru(NH_3)_5(NO_2)]^{+}$, 726
$RuH_{16}N_5O$
$[Ru(NH_3)_5(OH)]^{2+}$, 435
$RuH_{18}N_6$
$[Ru(NH_3)_6]^{3+}$, 28, 99, 190, 458, 471
RuN_4O_{10}
$Ru(NO)(NO_3)_3$, 938
$RuSiC_{33}H_{29}Cl_3N_6$
$[Ru(bipy)_2\{4\text{-Me-}4'\text{-}(Cl_3SiCH_2CH_2)bipy\}]^{2+}$, 25
$Ru_2C_6I_2O_6$
$Ru_2I_2(CO)_6$, 268
$Ru_2C_{24}H_{39}O_3$
$[Ru(C_6Me_6)_2(OH)_3]^{+}$, 304
$Ru_2C_{40}H_{36}N_8O_3$
$[\{Ru(bipy)_2(H_2O)\}_2O]^{4+}$, 529
$Ru_2C_{66}H_{59}P_4$
$[Ru_2H_4(PPh_2)(PPh_3)_3]^{2-}$, 233
$Ru_2H_{18}Cl_3N_6$
$[Ru_2Cl_3(NH_3)_6]^{2+}$, 571
$Ru_3C_{11}HO_{11}$
$[Ru_3H(CO)_{11}]^{-}$, 293
$Ru_3C_{12}H_{24}O_{16}$
$[Ru_3O(OAc)_6(H_2O)_3]^{+}$, 235
$Ru_3C_{22}H_{31}O_{10}Si_2$
$Ru_3H(SiEt_3)_2(CO)_{10}$, 293
$Ru_3C_{66}H_{63}O_{13}P_3$
$Ru_3O(OAc)_6(PPh_3)_3$, 234
$Ru_3H_{42}N_{14}O_2$
$[\{RuO(NH_3)_5\}_2Ru(NH_3)_4]^{6+}$, 1018
$[\{RuO(NH_3)_5\}_2Ru(NH_3)_4]^{7+}$, 498
$Ru_4C_{12}H_4O_{12}$
$Ru_4H_4(CO)_{12}$, 268

SbH_4O_4
$[Sb(OH)_4]^{-}$, 854
SbH_6O_6
$[Sb(OH)_6]^{-}$, 854
SbS_2
$[SbS_2]^{-}$, 853
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$[SbS_3]^{3-}$, 853
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$[SbS_4]^{5-}$, 853
Sb_2HS_4
$[Sb_2S_4H]^{-}$, 853
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$[SeF_6]^{3-}$, 854
ScH_2O_3
$ScO(OH)_2$, 360
SiF_6
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$SiFe_2C_{20}H_{18}Cl_2$
$\{FeCp(C_5H_4)\}_2SiCl_2$, 19
SiH_2O_4
$[SiO_4H_2]^{2-}$, 852
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SiO_4H_4, 852
$SiMo_{12}O_{42}$
$[SiMo_{12}O_{42}]^{8-}$, 529
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$[SiO_4]^{4-}$, 832, 845, 855
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$[Ru(bipy)_2\{4\text{-Me-}4'\text{-}(Cl_3SiCH_2CH_2)bipy\}]^{2+}$, 25
$SiW_{12}O_{40}$
$[SiW_{12}O_{40}]^{2-}$, 496
Si_2O_5
$[Si_2O_5]^{2-}$, 856
Si_2O_6
$[Si_2O_6]^{4-}$, 856
Si_2O_7
$[Si_2O_7]^{6-}$, 855
Si_3O_9
$[Si_3O_9]^{6-}$, 855
Si_3O_{10}
$[Si_3O_{10}]^{8-}$, 855
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$[Si_4O_{12}]^{8-}$, 855
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$[Si_4O_{13}]^{10-}$, 855
$SmC_8H_{11}NO_6$
$[Sm\{EtO_2CCH_2N(CH_2CO_2)_2\}]^{+}$, 422
Sm_2O_3
Sm_2O_3, 794
$SnCH_3O_6$
$[Sn(OH)_3(CO_3)]^{-}$, 854
$SnC_{10}H_{14}Cl_2O_4$
$Sn(acac)_2Cl_2$, 121
$SnC_{11}H_{22}O_2S$
$SnBu_2(O_2CCH_2CH_2S)$, 123
$SnC_{14}H_7Cl_3O_4$
Sn(2-hydroxyanthraquinon-1-olate)Cl_3, 86
$SnC_{14}H_{28}O_4S_2$
$SnBu_2(O_2CCH_2CH_2SH)_2$, 123
$SnC_{15}H_9Cl_3O_4$
$SnCl_3$(2-methoxyanthraquinon-1-olate), 55
$SnC_{16}H_{12}Cl_4O_4$
$SnCl_4$(1,2-dimethoxyanthraquinone), 55
$SnC_{36}H_{16}N_8O$
$\{Sn(phthalocyanine)O\}_n$, 151
$SnCl_6$
$[SnCl_6]^{2-}$, 292
SnF_3
$[SnF_3]^{-}$, 12
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$[SnF_6]^{2-}$, 12, 854
SnH_3O_3
$[Sn(OH)_3]^{-}$, 12
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$[Sn(OH)_6]^{2-}$, 4, 12
$SnPtC_{31}H_{32}Cl_4O_2P_2$
$PtCl(SnCl_3)$(diop), 266
$SnPtC_{36}H_{30}Cl_4P_2$
$PtCl(SnCl_3)(PPh_3)_2$, 248
$SnPtC_{36}H_{31}Cl_3P_2$
$PtH(SnCl_3)(PPh_3)_2$, 248, 263
$SnPtC_{37}H_{31}Cl_3OP_2$
$PtH(SnCl_3)(CO)(PPh_3)_2$, 263
$SnPtC_{40}H_{37}Cl_3OP_2$
$Pt(SnCl_3)(COPr)(PPh_3)_2$, 264
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$SnTcC_{12}H_{19}Cl_3N_6O_7$
$Tc(DMG)_3(SnCl_3)(OH)$, 974, 978

$TaC_{12}H_8N_2O_8$

$[Ta(O_2)_2(2\text{-}pyCO_2)_2]^-$, 329

$TaC_{24}H_{23}O_7$
$\{Ta(OPPh_2O)_2(OH)_3\}_n$, 1014

TaF_6
$[TaF_6]^-$, 813

TaF_7
$[TaF_7]^{2-}$, 813

$TcAs_4C_{20}H_{32}Cl_4$
$[Tc(diars)_2Cl_4]^+$, 978

$TcBr_4O$
$[TcOBr_4]^-$, 982

$TcCH_3O_7P_2$
$[Tc(O_3PCH_2PO_3)(OH)]^-$, 978, 987

$TcC_4H_4O_3S_4$
$[TcO\{SCH_2C(O)S\}_2]^-$, 976, 978, 982

$TcC_4H_8OS_4$
$[TcO(SCH_2CH_2S)_2]^-$, 978, 980, 981, 982, 984

$TcC_4H_8O_3S_2$
$[TcO(SCH_2CH_2O)_2]^-$, 978, 979, 982

$TcC_4H_8O_5$
$[TcO(OCH_2CH_2O)_2]^-$, 981, 982

$TcC_4H_{16}N_4O_2$
$[TcO_2(en)_2]^+$, 978, 980, 982

$TcC_4N_4O_2$
$[TcO_2(CN)_4]^{3-}$, 979, 981, 982

$TcC_4O_5S_4$
$[TcO(C_2O_2S_2)_2]^-$, 981

$TcC_5H_3N_4O_2$
$[TcO(OMe)(CN)_4]^{2-}$, 981, 982

TcC_5N_5O
$[TcO(CN)_5]^{2-}$, 981, 982

$TcC_6H_8N_2O_3S_2$
$[TcO(SCH_2CONCH_2CH_2NCOCH_2S)]^-$, 978, 979, 982

$TcC_6H_{12}OS_4$
$[TcO(SCH_2CH_2CH_2S)_2]^-$, 981

$TcC_6H_{24}N_{12}O_6$
$[Tc(H_2NCONH_2)_6]^{3+}$, 983, 991

$TcC_6H_{24}N_{12}S_6$
$[Tc(H_2NCSNH_2)_6]^{3+}$, 975

$TcC_6N_6S_6$
$[Tc(NCS)_6]^{3-}$, 983

$TcC_8H_8O_8S_4$
$Tc\{SCH(CO_2H)CH(CO_2H)S\}_2$, 989

$TcC_9H_{10}BCl_2N_6O$
$TcO\{HB(\overline{NCH{=}CHCH{=}N})_3\}Cl_2$, 975, 978

$TcC_{10}H_8ClN_2O_3$
$TcO_3(bipy)Cl$, 977

$TcC_{10}H_8Cl_3N_2O$
$TcO(bipy)Cl_3$, 978

$TcC_{10}H_{10}N_2O_2$
$[TcO_2(py)_2]^+$, 982

$TcC_{10}H_{12}N_2O_9$
$[TcO(edta)]^-$, 978, 982
$[TcO(edta)]^{2-}$, 978

$TcC_{10}H_{19}N_2O_5S_2$
$TcO\{SCMe_2CH(NH_2)CO_2\}\{SCMe_2CH(NH_2)CO_2H\}$, 978, 979, 982

$TcC_{10}H_{20}N_3S_4$
$TcN(S_2CNEt_2)_2$, 975, 978, 979, 982

$TcC_{10}H_{24}N_4O_2$
$[TcO_2(1,5,8,12\text{-tetraazacyclotetradecane})]^+$, 978, 980, 982

$TcC_{12}H_{12}N_2O_{14}$
$[Tc(\mu\text{-}O)\{N(CH_2CO_2)_3\}]_2$, 980

$TcC_{12}H_{20}N_2O_4$
$TcO(H_2O)\{MeCOCHC(Me){=}NCH_2CH_2N{=}CMeCHCOMe\}$, 978, 982

$TcC_{12}H_{32}Cl_2P_4$
$[Tc(Me_2PCH_2CH_2PMe_2)_2Cl_2]^+$, 975, 981, 990

$TcC_{12}H_{32}O_2P_4$
$[TcO_2(Me_2PCH_2CH_2PMe_2)_2]^+$, 975, 981, 982

$TcC_{12}H_{33}O_2P_4$
$[TcO(Me_2PCH_2CH_2PMe_2)_2(OH)]^{2+}$, 975, 982

$TcC_{13}H_9ClNO_3$
$TcO\{2\text{-}(2\text{-}OC_6H_4CH{=}N)C_6H_4O\}Cl$, 978, 979, 982

$TcC_{14}H_{25}N_4O_3$
$TcO\{N(O){=}CMeCHMeNCH_2CMe_2CH_2\text{-}NCHMeCMe{=}N(OH)\}$, 996

$TcC_{16}H_{14}ClN_2O_3$
$TcO(salen)Cl$, 978, 982

$TcC_{18}H_{28}N_3S_4$
$TcN\{S_2C{=}C(NHPr^i)(CH_2)_3\}_2$, 982

$TcC_{18}H_{36}N_2O_2P_2$
$Tc(PMe_3)_2\{MeCOCH(Me){=}NCH_2CH_2N{=}CMeCHCOMe\}$, 996

$TcC_{18}H_{48}P_6$
$[Tc(Me_2PCH_2CH_2PMe_2)_3]^+$, 975

$TcC_{18}H_{54}O_{18}P_6$
$[Tc\{P(OMe)_3\}_6]^+$, 983

$TcC_{20}H_{16}ClN_2O_3$
$TcO(2\text{-}Me\text{-}8\text{-}quinolinolate)_2Cl$, 978, 982

$TcC_{20}H_{20}N_4O_2$
$[TcO_2(py)_4]^-$, 981

$TcC_{20}H_{28}$
$[Tc(1,2,3,5\text{-}Me_4C_6H_2)_2]^+$, 996

$TcC_{24}H_{33}Cl_2NP_3$
$TcN(PMe_2Ph)_2Cl_2$, 978

$TcC_{25}H_{33}Cl_3OP_3$
$Tc(CO)(PMe_2Ph)_3Cl_3$, 977

$TcC_{30}H_{54}N_6$
$[Tc(CNBu^i)_6]^+$, 991
$[Tc(CNBu^t)_6]^+$, 983, 990

$TcC_{36}H_{30}Cl_2NP_2$
$TcN(PPh_3)_2Cl_2$, 982

$TcC_{40}H_{33}N_4P_2S_2$
$TcN(PPh_3)_2(MeCN)(NCS)_2$, 982

$TcC_{42}H_{66}N_6O_{12}$
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$Tc_2C_{12}H_{12}N_2O_{14}$
$[Tc(\mu\text{-}O)\{N(CH_2CO_2)_3\}]_2$, 974

$Tc_2C_{20}H_{28}N_4O_{18}$
$[Tc(\mu\text{-}O)\{O_2CN(CO_2H)CH_2CH_2N(CO_2H)CO_2\}]_2$, 980

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$Zr(OH)(NO_3)\{OP(O)(OBu)_2\}_2$, 953
$ZrC_{32}H_{74}N_2O_{22}P_4$
$Zr(NO_3)_2\{HOP(O)(OBu)_2\}_2\{OP(O)(OBu)_2\}_2$, 944
ZrF_6
$[ZrF_6]^{2-}$, 854, 927
$ZrHN_3O_{10}$
$Zr(OH)(NO_3)_3$, 943
$ZrH_2N_2O_8$
$Zr(OH)_2(NO_3)_2$, 943
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$Zr(NO_3)_4$, 812
$ZrTcN_3O_{13}$
$Zr(NO_3)_3(TcO_4)$, 945
$Zr_3H_4O_4$
$[Zr_3(OH)_4]^{8+}$, 812
$Zr_4H_{40}O_{24}$
$[Zr(OH)_2(H_2O)_4]_4^{8+}$, 943