Coordination Chemistry Reviews
Elsevier Publishing Company, Amsterdam – Printed in The Netherlands

THE COORDINATION CHEMISTRY OF METALLOPORPHYRINS

PETER HAMBRIGHT

Department of Chemistry, Howard University, Washington, D.C. 20001 (U.S.A.)

(Received June 29th, 1970)

CONTENTS

ABBREVIATIONS

CO	Carbon monoxide	MP	Metalloporphyrin
DA	Diacetyldeuteroporphyrin	P	Porphyrin
ETIO	Etioporphyrin	PP	Protoporphyrin
HP	Hematoporphyrin	Py	Pyridine
Im	Imidazole	TPP	Meso-tetraphenylporphin

A. INTRODUCTION

The coordination chemistry of metalloporphyrins is of continuing interest due to their role in energy transport and respiration systems, and because of the wide variety of metal ions that can be bound or chelated by the four coordinate macrocyclic porphyrin ligand, as noted in Fig. 1. Fig. 2 sketches the major reactions that involve porphyrins and metal ions, and such will be the subject of this paper. Various aspects of porphyrin and metalloporphyrin chemistry have been reviewed elsewhere [1–10].

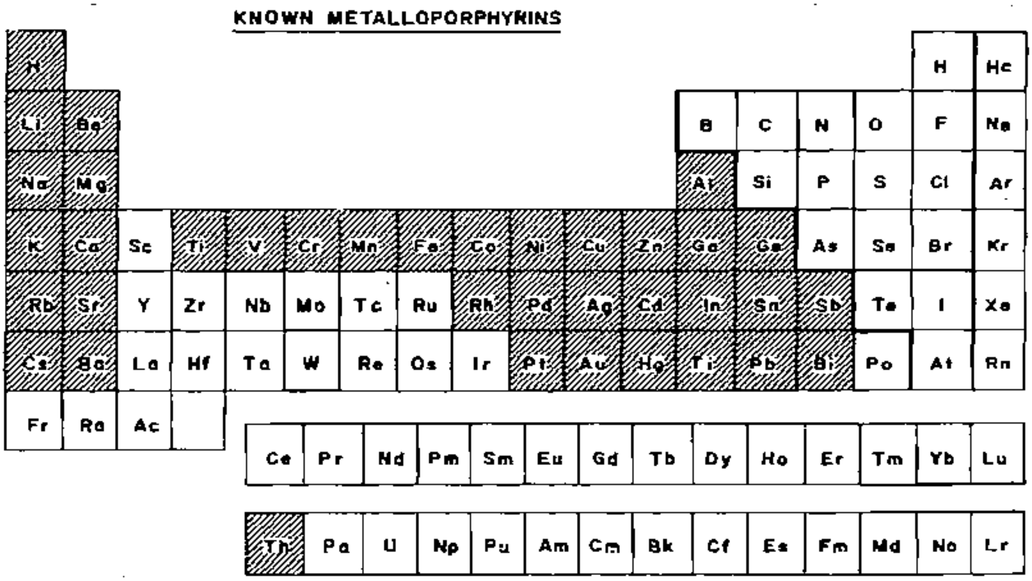


Fig. 1. The shaded elements are known to form adducts with various porphyrin molecules.

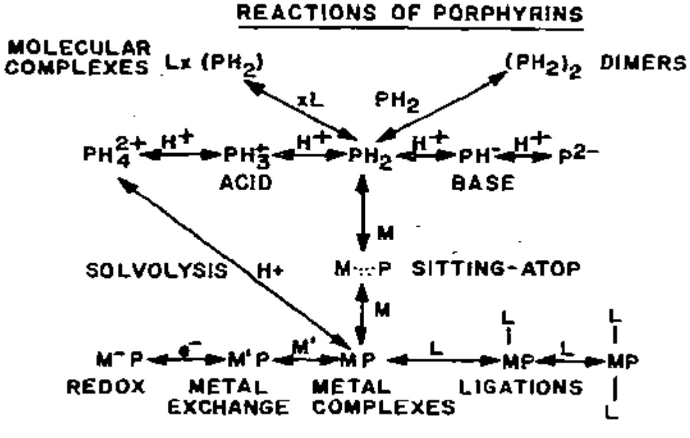
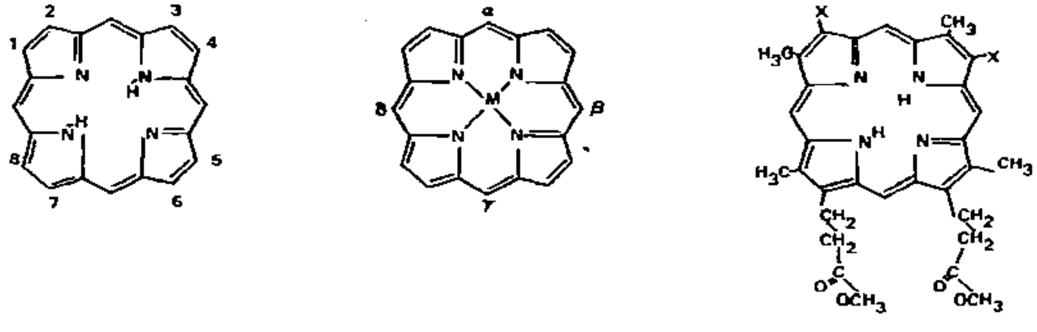


Fig. 2. Typical reactions and species found with porphyrins and metalloporphyrins.

B. PORPHYRIN TYPES AND STRUCTURES

The simplest porphyrin type, named porphin, is shown in Fig. 3. This cyclic conjugated tetrapyrrole pigment by the loss of the two central protons and the addition of a metal ion forms a metalloporphyrin. The most frequently studied porphyrin systems can be considered as being formally derived from the porphin framework. Thus the readily synthesized tetraphenyl-[11] or tetrapyridyl porphins [12,13] have four phenyl or *p*-pyridyl groups in the meso ($\alpha, \beta, \gamma, \delta$) positions of porphin, whereas octaethylporphin [14] contains eight ethyl groups in positions 1–8 of the porphin structure. The hydrogen atoms in the 2 and 4 positions of deutero-porphyrin IX dimethyl ester can be readily replaced by a variety of classical electrophilic substitution reactions [1,15] forming a substituted deuteroporphyrin series which exhibits a valuable trend in physical properties [6,16]. The members of this series are referred to by [6] trivial names as mesoporphyrin, protoporphyrin, etc. The syntheses of porphyrins and related oxidized and reduced species have been recently reviewed [17]

A number of detailed X-ray crystal structures of various porphyrins have been determined, and the work reviewed by Hoard [8] and Fleischer [9]. These molecules have been shown to be quite flexible, with both ruffled and planar skeletons observed. The great flexibility of the porphyrin nucleus is also shown by the synthesis of *N*-mono-[18,19] and *N, N*-dimethyl derivatives [20,21] and by the separation of the four statistically expected isomers of meso-tetra-*o*-hydroxyphenylporphin, which result from hindered rotation about the aryl–porphyrin bonds [22]. When placed in methanol, the most abundant isomer will interconvert to the others, at about ten times the rate as that of the corresponding hydrated copper derivative. This indicates that the porphyrin is capable of extreme distortion in solution, as such rotations are sterically impossible for a planar porphyrin nucleus. The slower rate of the copper derivative was attributed to its greater rigidity. The enthalpy for the formation of porphin leads [133] to a high resonance stabilization energy of about 400 kcal/mole.



PORPHIN METALLOPORPHIN 2,4 - disubstituted deuteroporphyrin IX dimethylester

Fig. 3. Structures of several typical porphyrins and metalloporphyrins.

C. ACID–BASE EQUILIBRIA

Porphyrins are amphoteric molecules which can add two protons to the free base (PH_2) imine type nitrogen atoms forming mono- (PH_3^+) or di-cations (PH_4^{2+}), and are capable of loosing two pyrrole type protons to form the mono- (PH^-) or di-anions (P^{2-}). Such equilibria in solution are denoted by pK values as follows [3,6]

$$PH_4^{2+} \underset{H^+}{\overset{pK_4}{\rightleftharpoons}} PH_3^+ \underset{H^+}{\overset{pK_3}{\rightleftharpoons}} PH_2^+ \underset{H^+}{\overset{pK_2}{\rightleftharpoons}} PH^- \underset{H^+}{\overset{pK_1}{\rightleftharpoons}} P^{2-}$$

The equilibria are usually determined from changes in the characteristic absorption spectra of the species upon titration with acids or bases. There is evidence for each type in solution, but not necessarily with a given porphyrin. The aqueous phase insolubility of many porphyrins has led to titrations in non-aqueous solution and phase distribution studies to elucidate the equilibria [6]. The simultaneous dissociation of carboxylic acid side chains and field effects caused by positive and negative peripheral substituents complicates the determination of intrinsic dissociation constants [23]. For example most carboxylic acid containing porphyrins require stronger bases than hydroxide to form P^{2-}, while due to the positive field of four *N*-methyl pyridyl groups on the tetra-*N*-methylated tetrapyridylporphin, a pK_3 of 11.6 is observed [24].

An important advance has been in the use of detergents to monomerize and solubilize porphyrins in aqueous solution [25]. Self-consistent pK_3 values have been tabulated for numerous substituted deuteroporphyrins [6,16], showing that electron-donating substituents on the periphery of the porphyrin increase its apparent basicity. With anionic and neutral detergents both pK_3 and pK_4 can be determined, while cationic detergents destabilize PH_3^+, allowing only the product K_4K_3 to be obtained [25]. The fact that both PH_3^+ and PH_4^+ are observed in absolute ethanol with HCl whereas only the PH_2—PH_4^{2+} equilibria is found in absolute chloroform [26], indicates the solvent dependence of the reactions.

On the basis of the extremely non-planar porphyrin nuclei found in diacid species of tetrapyridyl- and tetraphenylporphins in the solid state, compared to their relatively planar free base structures, Stone and Fleischer [27] have accounted for the limited existence of PH_3^+ in aqueous solutions of these porphyrins [28] in the following way. Upon incorporation of the first proton into the relatively planar PH_2 (having its unshared pairs directed inward), a non-planar PH_3^+ species is formed, with its opposite pyrrole groups tilted alternately upwards and downwards. The second proton can thus readily protonate the now accessible non-bonded pair, and form the diacid. The energetics are the reverse of that shown by most dibasic acids, where the barrier for the second proton addition is usually larger than the first.

D. METAL COMPLEXES

Fig. 1 indicates the metal ions that have been found to form compounds with porphyrin molecules. Treibs [29] gives details on the preparation of Mn^{II}, Co^{II}, Co^{III}, Pd^{II}, Pt^{II}, Cd^{II}, Ag^{II}, Hg^{II}, Pb^{II}, Al^{III}, Ga^{III}, In^{III}, Ge^{IV}, Sn^{IV}, Sb^{III} and Bi^{III} complexes of substituted deuteroporphyrins. A similar series of meso-tetraphenylporphin complexes including Ni^{II}, Cu^{II}, Zn^{II}, Fe^{III} and the alkali metals have been reported [30,31]. A number of special techniques have been given in the monograph by Falk [6], and the preparations of dipyridine Fe^{II} [32], Fe^{III} with various ligands [33], Mg^{II} [34], Au^{III} [35], Mn^{III} [36,37], Si^{IV} [38] and Ge^{IV} [39] porphyrins are of note. The IR and mass [134] spectra of many metalloporphyrins [40] and free base ligands [15] have been determined. Sc, Zr and Mo porphyrins are also known [135,136].

Much current interest has centered on the synthesis of previously unpreparable metalloporphyrins by the use of metal carbonyl and organometallic substrates. Thus $[Rh(CO)_2Cl]_2$, $[Ir(CO)_3Cl]$ and their cyclooctene derivatives form six coordinate Rh^{III} porphyrins and Ir^{III} species with a strongly bonded CO group [41]. A phenyl $rhodium^{IV}$ meso-tetraphenylporphin (TPP) with a rhodium-carbon σ bond has also been prepared [42]. $Cr(CO)_6$ and diphenyltitanium were used to form chromium and titanyl complexes [43]. The problem with porphyrins is that the macrocycle cannot be condensed about a given metal ion as readily as in the phthalocyanine series [44]. The template hypothesis applied to porphyrin synthesis has not met with great success [12,13].

Following the preparation of an oxy-bridged manganese dimer in the phthalocyanine series [45], several groups have synthesized and studied the properties of the corresponding oxy-bridged manganese [46] and iron porphyrin dimers [33,47,48]. The Fe—O—Fe angle in a TPP derivative was shown to be 168°, and antiferromagnetic interactions between the iron atoms were noted [47,48]. The kinetics of formation and dissociation of the dimers is known [46].

Complete X-ray crystal structures of a number of metalloporphyrins have been determined [9]. The five coordinate metal ions in metalloporphyrins (H_2OMg, H_2OZn, $V^{IV}O$, $ClFe^{III}$) lie from 0.2 to 0.5 Å above the porphyrin plane towards the ligand. Four (Ni, Cu) or six ($(imidazole)_2Fe^{III}$) coordinate metal ions are centered approximately in the porphyrin plane. Storm [49] has developed a proton magnetic resonance analysis to determine the in plane – out of plane distances of metal ions in metalloporphyrin – pyridinates in solution. His method depends on the relative chemical shifts of coordinated pyridine protons, which are influenced by the porphyrin ring current. It was suggested that cobalt is in the plane in $(Py)_2Co^{III}P$, whereas the species Py—ZnP and Py—MgP have their ions 0.2—0.8 Å above the plane.

Reich and Cohen [50] have prepared a ferric porphyrin using $C(CN)_3^-$ as the anion. The single IR active band found for the anion showed that it did not distort from planar in the complex, and was interpreted to indicate a lack of covalent character in the Fe—C bond.

Complexes of Zn—TPP in which one or two tricarbonyl-chromium groups are π-substituted on the phenyl rings are known and other first row transition ions were reported to form similar species [51]. While porphyrins are apparently absent from the lunar surface, a novel cosmochemical synthesis has been proposed [52].

The reactions of alkyl and aryl magnesium bromides with pyridinobromo Co^{III} etioporphyrin produce aquo alkyl and aryl cobalt complexes [53]. Other acyl or aryl Co^{III} species are produced from Co^{I} porphyrins with acyl or aryl halides. *p*-Tolyl and ethyl Fe^{III} porphyrin species have also been described [48,53]. A Ni^{III}TPP cation has been characterized, as well as a number of transition metal paramagnetic cation radical or metal-center complex ions of metalloporphyrins [137].

While most porphyrins and metalloporphyrins are purified by recrystallization, siloxygermaniumporphyrins [39] and tetraphenylporphins [11] readily sublime. Bis(trimethylsiloxy) Si^{IV} etioporphyrins have been separated from other species by gas chromatography [38]. Sublimation of unsymmetrically substituted etioporphyrins, however, leads to rearranged products [54]. Gel filtration techniques have been used to separate porphyrins of approximately the same molecular weights [55].

TABLE 1

Selected magnetic susceptibilities of metalloporphyrins *

System	Complex **	Coordination number	μ_{obs} (B.M.)	Temperature range ***	Unpaired electrons	References
d^9	Cu^{II}–HP	4	1.93	N	1	57
	Ag^{II}–HP	4	1.94	N	1	57
d^8	Ni^{II}–HP	4	0	N	0	57
	Ni^{II}–DA$(Py)_2$	6	3.45	RS	2	59
	Pd^{II}–HP	4	0	N	0	57
	Pt^{II}–ETIO	4	0	R	0	57
d^7	Co^{II}–MP	4	2.89	N	1	57
d^6	Co^{III}–HP(OH_2, Cl)	6	0.23	N	0	57
	Rh^{III}–MP(Cl, OH_2)	6	0.05	R	0	41
	Fe^{II}–PP$(OH_2)_2$	6	4.83–5.02	RS	4	129
	Fe^{II}–PP(Py, CO)	6	0	RS	0	80
	Ir^{III}–HP(CO, Cl)	6	0	R	0	41
d^5	Fe^{III}–PP(Cl)	5	5.88	N	5	64
	Fe^{III}–TPP$[Cl, (Im)_2]$	6	2.36	H	1	130, 131
	Mn^{II}–HP$(Py)_2$	6	5.9	RS	5	132
	Rh^{IV}–TPP(C_6H_5Cl)	6	1.95	R	1	42
d^4	Mn^{III}–HP(Cl, OH_2)	6	4.88	N	4	57, 132
	Cr^{II}–MP	?	2.84	R	?	43
	Cr^{II}–MP	4	5.19	RS	1	43
d^3	Mn^{IV}–HP$[(OH_2)_2]$	6	2.0	RS	1	132
d^1	$V^{IV}O$–HP	5	1.79	N	1	57
d^0	$Ti^{IV}O$–MP	5	0	R	0	43

* See Refs. 56 and 57 for earlier work.

** For abbreviations see p. 247.

*** R = ambient temperature; N = 80–300°K; H = 4.2–50°K; S = solution.

E. MAGNETIC SUSCEPTIBILITIES

Magnetic susceptibility measurements have always been important in determining the oxidation states of metal ions in biological compounds [56], and Table 1 shows representative data on porphyrin systems [57]. Of particular interest are recent studies on Ni^{II} porphyrins by ^1H NMR techniques [58]. The four coordinate planar Ni^{II} porphyrins are diamagnetic [59], while five or six coordinate species formed by the addition of nitrogenous bases to the axial positions in solution become paramagnetic. Co^{II} porphyrins show a decrease in moment when going from four to six coordination [60]. The explanation appears to be an oxidation to Co^{III} rather than a reduction in orbital contribution for the higher coordinated Co^{II}.

A number of iron proteins and inorganic complexes show spin-state equilibrium behavior, and such has been noted in bispyridino iron(III) protoporphyrin systems [61]. These complexes are reported to show $S = {}^5/_2$ states at room temperature dropping to $S = {}^1/_2$ states below 200°K. A linear relationship was found between the basicity of the coordinated pyridines and the paramagentic chemical shifts of the protons on peripheral methyl groups of the low-spin forms. Similar work has been reported for low-spin cyanohemins [62] and various axial ligand substituted high-spin deuterohemins [63], with emphasis on a π-delocalization of spin mechanism.

Several workers have reported room temperature moments ranging from 1.15 to 2.68 B.M. for the oxy-bridged porphyrin dimers, in various states of purity and hydration [47,48]. The moments drop to almost zero below 77°K, which could indicate iron–iron interaction. The presence of such dimers was suggested as an explanation of the significantly lower than spin-only moments found over the years with other high spin Fe^{III} porphyrins in solution [56].

The magnetic susceptibility of hemin (chloro-Fe^{III} protoporphyrin IX) and other ferric porphyrins have been measured from 300–4°K by several groups [64,65]. The susceptibilities were found to deviate appreciably from the Curie law below 20°K, presumably a reflection of the populations of the zero field states. Far IR techniques [66] have been used to directly measure the zero field splittings, $2D$. The Kotani equation [67], which gives the temperature variation of the susceptibility with $2D$, was unable to reproduce the observed susceptibility data. Low temperature Mössbauer studies [68], however, are compatible with the observed $2D$, and no satisfactory explanation for this anomalous behavior has been advanced. The hemin data can be reproduced with the empirical equation [64]

$$\chi_g = C/(T+\epsilon)$$

with $\epsilon = 3.1$°K and $C = 7.09 \times 10^{-3}$.

F. STABILITY CONSTANTS

Many metal ions in metalloporphyrins are able to add one or two Lewis base ligands to form five coordinate approximate square pyramid or six coordinate pseudo-octahedral species in solution. Such equilibria have been probed

$$\mathrm{MP} \underset{\mathrm{L}}{\overset{K_1}{\rightleftharpoons}} \mathrm{MP{-}L} \underset{\mathrm{L}}{\overset{K_2}{\rightleftharpoons}} \mathrm{MP{-}L_2}$$

by shifts in the porphyrin absorption bands, chemical shifts of the coordinated ligand or porphyrin protons, or changes in the potential of the coordinated metal ion. Whatever the method, the problem of porphyrin aggregation and especially dimerization exists. Such association has been the topic of many ESR [69], NMR [70], electrochemical [71], spectral and sedimentation studies [6]. A complicated interplay of factors determine aggregation. For example polarographic work has shown that Fe^{II} and Fe^{III} protoporphyrins are dimerized in basic solution [71] while the corresponding hematoporphyrin complexes (having 2–4 dihydroxyethyl rather than vinyl groups) are monomeric [72]. In general increased porphyrin basicity, more ionized side chains, lower concentrations in solution, the presence of coordinating or solvating agents and detergent solutions favor monomers over dimers [73]. From

ESR data, a stability constant of $10^4\ M^{-1}$ has been estimated for Cu uroporphyrin dimerization, compared to $10^8\ M^{-1}$ for phthalocyanines [74]. Mackly and Akeson [75] measured the hemin dimer equilibrium

$$[\mathrm{Fe^{III}P(OH_2)_2}]_2 + 4\ \mathrm{EtOH} \rightleftharpoons 2\ \mathrm{Fe^{III}P{\cdot}(EtOH)_2} + 2\ \mathrm{H_2O}$$

and found that at pH = 7, 5.6 M ethanol is needed to half dissociate the dimer. IR studies show that vanadyl porphyrins associate [138]. At pH 6 the equilibrium constant for the monomer–dimer association of a water-soluble porphyrin was $7.5 \times 10^5 M^{-1}$. From T-jump studies the forward rate constant was $7.8 \times 10^7\ M^{-1}\ \mathrm{sec}^{-1}$, with a reverse constant of 110 sec^{-1} [139].

The stability constants [76] of the 1:1 complexes formed between the divalent tetraphenylporphin complexes and pyridine fall in the order Zn > Cd > Hg > VO, Cu. For Zn, Cd, and Hg, the constants show linear $\log K - \mathrm{p}K$ correlations with the basicity of the *para*-substituted pyridine, and an interesting Hammett relationship of the form

$$-\log K/K_0 = \rho\sigma$$

K_0 is the stability constant for pyridine, K for the substituted pyridine with σ its substituent constant, and ρ is the reaction sensitivity parameter. For Zn, Cd and Hg, ρ was in the order 1.5, 2.2 and 3.1, respectively, indicating that the Hg reactions are more sensitive to substituent effects from pyridine than are Zn or Cd. The interpretation was that $\mathrm{Hg^{II}}$ accepted more of the electron pair from a given pyridine ligand than did $\mathrm{Zn^{II}}$, causing the pyridine nitrogen adjacent to $\mathrm{Hg^{II}}$ to bear a higher formal positive charge. Thus the Hg reactions would be more sensitive to p-substituent donor effects than Zn reactions. Apparently ρ parallels the sigma polarizability of the metal ion, and its class a or b character. Differential thermal analysis studies [77] showed that the thermal removal of pyridine type ligands from metalloporphyrins in the solid state followed the same trends as the stability constants in solution. Higher liberation temperatures were found when the substituted pyridine basicity or charge:radius ratio of the cation was increased and when porphyrin basicity was decreased. Thermal studies with a vacuum microbalance have shown that acetato $\mathrm{Mn^{III}}$ etioporphyrin adds one mole of pyridine to form a six-coordinate structure in the solid state. When sublimed onto an optical cell, the $\mathrm{Mn^{II}}$ species is produced, which rapidly oxidizes in air [78].

Spectrophotometric studies showed that $\mathrm{Ni^{II}}$ porphyrins add two nitrogenous base ligands, with no evidence for 1:1 species [59]. As found with Zn, the less basic the porphyrin or the more basic the axial ligands, the more stable was the diligated adduct. In contrast, ^{1}H NMR studies showed that $\mathrm{Ni^{II}}$ mesoporphyrin adds only one piperidine ligand in solution [58], and further comparison of the two methods should be rewarding.

As with $\mathrm{Ni^{II}}$, $\mathrm{Fe^{II}}$ porphyrins in detergent solutions were shown to form only 1:2 complexes [79,140]. In contrast to Zn and Ni, the $\mathrm{Fe^{II}}$ porphyrin stability constants increased with substituted porphyrin basicity and decreased with an increasing substituted pyridine basicity. This trend in $\mathrm{Fe^{II}}$ porphyrin behavior has been attributed to its ability to π-bond with axial ligands. Many lines of evidence support the π-bonding hypothesis: the stability and existence of mixed ligand complexes (CO–Py and $\mathrm{CN^-}$–Py) compared to dipyridinates [80], the increased stability of CO–$\mathrm{Fe^{II}P}$–Py complexes with increased basicity of the porphyrin and pyridine, and the increase in the CO stretching frequency with decrease in porphyrin basicity [81]. The oxygen affinities of reconstituted hemoglobins and myoglobins follow similar trends, suggesting that a π-bonded O_2 parallel to the porphyrin plane is more probable than an end-on σ-type configuration [79,140].

The first association constant of Mg^{II} porphyrins with pyridine is so high that only the five to six coordinate ligation can be measured [82]. The association constants for this process were found to be rather independent of porphyrin and ligand basicity. It was suggested [59] that as porphyrin basicity decreases, the ligand binding in the five- as well as six-coordinate structures are strengthened, with the result that no basicity effect will be shown for the five to six ligation. The α protons of pyridines coordinated to Mg and Zn porphyrins [83] show high field shifts due to the porphyrin ring current; however solvent—solute interactions have precluded the calculation of stability constants. The exchange of coordinated pyridine is facile in both systems, as shown by the absence of line broadening at low temperatures.

Phillips [3] has reinterpreted and reviewed the earlier work on the equilibria of Fe^{II} and Fe^{III} porphyrins in aqueous solution. Such studies are complicated by the dimerization of iron species containing at least one axial hydroxide or water ligand. There appears to be no evidence for dimerization in manganese or cobalt systems and the trivalent states as well as divalent Mn appear to add two ligands. The electrode potentials of manganese porphyrins vary with the axial ligand, and porphyrin type [141]. Co^{II} porphyrins are anomalous in that when placed in solvents above a certain dielectric constant, fairly rapid oxidation to Co^{III} occurs [84,85]. In toluene glasses, ESR work shows five or six coordination hy amines can occur with Co^{II} porphyrins, and the existence of amine—CoP—O_2 adducts was demonstrated [142]. Coboglobins also reversibly bind molecular oxygen [143].

Caughey [59,73] has shown how much of the stability constant data and the trends in the physical properties (adsorption band positions, zero field splittings, quadrupole splittings) of ferric porphyrins can be explained by assuming that a stronger porphyrin-to-metal-ion bond means a weaker metal-ion-to-ligand bond. For example the enthalpies of ligand association were found to increase with a decrease in porphyrin basicity for the Ni^{II} series.

Porphyrins also form molecular complexes. Benzylviologen forms a very stable 1:1 complex with hematoporphyrin [86]. Mauzerall [74] has shown that many planar neutral heterocyclic bases and large organic cations form a series of molecular complexes with uroporphyrins.

G. MECHANISMS OF METAL ION INCORPORATION

A number of studies have dealt with the problem of how metal ions are incorporated into porphyrin molecules

$$M^{2+} + PH_2 \rightleftharpoons MP + 2\,H^+$$

While it is obviously necessary for the metal ion to loose much of its solvation sphere and the porphyrin to release its two central protons, the sequence of these changes is not as yet clear. The problem of the lack of solubility of porphyrins in aqueous media has been circumvented by using water-soluble derivatives, detergent solutions or mixed solvents.

The kinetics of Cu^{II} incorporation into the water-soluble 2,4-disulphonated deuteroporphyrin dimethyl ester in acidic and neutral solutions followed a rate law[87],

$$d[CuP]/dt = kK[PH_2][Cu]/(K + [H^+])$$

in accord with the mechanism

$$PH_3^+ \rightleftharpoons PH_2 + H^+ \quad K$$

$$Cu^{2+} + PH_2 \rightarrow CuP + 2\,H^+ \quad k$$

No evidence was found for direct incorporation into PH_4^{2+} or PH_3^+, presumably due to electrostatic factors, and the directly measured K was in agreement with that from the kinetic analysis.

With hematoporphyrin in basic solution, both Cu and Zn were incorporated in terms of the mechanism

$$M(OH)_4^{2-} \rightleftharpoons M(OH)_3^- + OH^- \qquad K$$

$$M(OH)_3^- + PH_2 \rightleftharpoons MP + 2\,H_2O + OH^- \qquad k$$

The predissociation of $Zn(NH_3)_4^{2+}$ and $Zn(CN)_4^{2-}$ into the triligated species before insertion indicates the importance of the geometry of the metal–ligand reactant[88,89]. Similarly only the 1:1 and not the 1:2 Cu–oxine complex was active in incorporation[90].

The details of the incorporation process have been viewed in terms of either an S_N1 mechanism

$$PH_2 \rightleftharpoons P^{2-} + 2\,H^+$$

$$M^{2+} + P^{2-} \rightleftharpoons MP$$

or an S_N2 scheme

$$M^{2+} + PH_2 \rightarrow [M \,..\, PH_2] \rightarrow MP + 2\,H^+$$

The basis for the speculations were rate laws of Cu^{II} insertion which were first-order in metal ion and porphyrin. At that time, there was no strong evidence that species with reduced or increased coordination numbers existed at that pH so the fact that, in a series of porphyrins, the rates increased with porphyrin basicity led to an assignment of an S_N2 mechanism.

In methanol–chloroform solutions, Fleischer and Wang[91] found evidence for a 1:1 monomeric complex between $FeCl_3$ and protoporphyrin, which they called a sitting-atop (sat) complex. This species lent weight to the S_N2 argument. The complex was postulated as being dimeric in pure chloroform, and was dissociated by high concentrations of alcohol or pyridine. On the basis of certain shifts in the absorption spectra of the porphyrin in acetone solution upon the addition of metal ions, evidence was obtained for Fe^{II}, Fe^{III}, Cr^{III}, Pt^{IV}, Sn^{II}, Zn^{II}, V^{IV} and U^{VI} sitting-atop species. Certain of these sitting-atop porphyrins formed metalloporphyrins upon heating. The crystal structure of a presumed sitting-atop complex[27] was later shown to be the diacid derivative $[H_4P^{2+}Cl^-(FeCl_4)^-]$.

When the sitting-atop entity was postulated, it was noted that its spectra resembled that of diacid derivatives[4], and Burnham and Zuckerman[26] have presented evidence that the sitting-atop species in non-aqueous solution are in fact salts formed between the diacid porphyrin and anions of the solvated metal ion. For example, it was suggested that Fe_2Cl_6

is solvolyzed by ethanol as follows:

$$Fe_2Cl_6 + 2\,EtOH \rightarrow Cl^- + 2\,H^+ + [Fe_2Cl_5(OEt)_2]^-$$

Two released protons would form PH_4^{2+} from PH_2, with two solvolyzed mononegative dimers acting as gegenions.

In aqueous solution, the water soluble meso-tetrapyridylporphin forms 1:1 adducts with a wide variety of mono-, di- and tri-valent cations [92] having stability constants ranging from 1.5 for K^+ to 85 for Fe^{3+}. The kinetics of incorporation of the divalent ions followed a rate law of the form

$$d[MP]/dt = \frac{kK_{sat}K'_{sat}[M]^2[PH_2]}{[H^+](1 + K_{sat}[M] + K_d[H^+]^2)}$$

The assumed mechanism, in terms of the observed sitting-atop species ($M\text{-sat-}PH_2$) was

$$PH_2 + 2\,H^+ \rightleftharpoons PH_4^{2+} \quad K_d$$

$$PH_2 + M_a \rightleftharpoons M_a\text{-sat-}PH_2 \quad K_{sat}$$

$$M_a\text{-sat-}PH_2 \rightleftharpoons M_a\text{-sat-}PH^- + H^+ \quad K'_{sat}$$

$$M_a\text{-sat-}PH^- + M_b \rightleftharpoons M_bP + H^+ + M_a \quad k$$

the constant kK'_{sat} could be extracted and the order for the ions was Cu > Zn > Mn > Co > Fe > Ni > Cd. While the reaction scheme assumed that the inverse proton dependence arose from a metal ion assisted porphyrin proton dissociation, the equilibria

$$M(H_2O)_x \rightleftharpoons M(H_2O)_{x-1}(OH)^- + H^+$$

could not be excluded. The notable feature was that two metal ions were required for the incorporation process, and it was impossible to tell if the sitting-atop cation (M_a) or another (M_b) was the one incorporated since M_a and M_b were the same.

In a recent study [93], the rates of incorporation of Zn and Cu into this porphyrin as a function of Li^+ were measured. Li^+ forms a sitting-atop species but not a metalloporphyrin. A two term rate law was found; one term was second order in Zn, the other first order in Zn and Li. The indication was that the sitting-atop ion was not the one that inserted.

Cr^{3+} formed a sitting-atop species having a stability constant similar to other trivalent ions [92]. Since Cr^{3+} is substitution inert, and tetrapyridylporphin rather flexible, the sitting-atop species may have water molecules trapped between the cation and porphyrin, explaining why the sitting-atop cation does not simply drop into the porphyrin. Another view of sitting-atop species is that they are stacked planes of tetrapositive porphyrin molecules stabilized by nitrate anions [74].

Meso-tetrapyridylporphin does not form sitting-atop species in acetic acid — water mixtures [94], and the rates of insertion were first order in metal and porphyrin, in the order

Cu > Zn > Co > Ni. The copper rate showed an inverse dependence on hydrogen ion activity, which was unexplained as the porphyrin had no known dissociation equilibria in the range studied. The rates showed a curious dependence on acetic acid concentration, with a minimum at 50% and maximum at about 90%, which was attributed to a mixed copper coordination sphere.

Plane and coworkers have shown that Mg and Zn incorporation is catalyzed by nitrogenous bases. For the Zn study [95] at constant pH the rate law was

$$\text{rate} = k[\text{Zn}][\text{PH}_2] + k'[\text{Zn}][\text{PH}_2][\text{B}]$$

with B as pyridine, methyl substituted pyridines or imidazole. The fact that 2,6-dimethylpyridine was catalytically inactive was evidence for the coordination of the bases to Zn during the process, whose rate increased with ligand basicity.

For the Mg study in methanol [96], the rate law found was

$$\text{rate} = k_1 [\text{PH}_2]/[\text{H}^+] + k_2 [\text{PH}_2][\text{Mg}][\text{pyridine}]/[\text{H}^+] .$$

Due to the inherent limitations in the kinetic method, the two formulations for the uncatalyzed paths

$$\text{BH} \rightleftharpoons \text{B}^- + \text{H}^+$$

$$\text{B}^- + \text{PH}_2 \rightleftharpoons \text{PH}^- + \text{BH} \quad \text{slow}$$

$$\text{PH}^- + \text{Mg} \rightarrow \text{MgP} + \text{H}^+ \quad \text{fast}$$

$$\text{B}^- = \text{base } (\text{OH}^-, \text{CH}_3\text{O}^-, \text{etc.})$$

and

$$\text{PH}_2 \rightleftharpoons \text{PH}^- + \text{H}^+$$

$$\text{PH}^- \rightleftharpoons (\text{PH}^-) \quad \text{slow}$$

$$(\text{PH}^-) + \text{Mg} \rightarrow \text{MgP} + \text{H}^+ \quad \text{fast}$$

could not be distinguished. Both mechanisms place emphasis on a dissociative, rather than metal ion associative mechanism. For the catalyzed path, the proposed sequence was

$$\text{Py} + \text{Mg} + \text{PH}_2 \rightleftharpoons \text{Py{-}Mg{-}PH}_2$$

$$\text{Py{-}Mg{-}PH}_2 \rightleftharpoons \text{Py{-}Mg{-}PH}^- + \text{H}^+$$

$$\text{Py{-}Mg{-}PH}^- \rightarrow \text{Py{-}Mg{-}P} + \text{H}^+$$

The dissociation of a porphyrin proton from a magnesium–pyridine–porphyrin complex, similar to that in the sitting-atop reaction, was postulated. Since Mg is one of the slowest of all ions to be incorporated, it was suggested [96] that pyridine was necessary to change the coordination sphere of Mg to make it of comparable reactivity, in this associative process.

The charge on the porphyrin and its environment affect the incorporation rates. Thus with Fe^{II} in 10% pyridine at constant pH, the rates increased with the number of negatively charged carboxylic acid groups on the porphyrin, being 8, 4, and 2 for uro-, copro- and hemato-porphyrin [86]. The rates spanned a 370-fold range, and arose from an activation entropy term. This was viewed as an increasing number of negative acid functions progressively stabilizing a sitting-atop activated complex. Similarly the rate of Cu incorporation into the dinegative disulphonic acid porphyrin was over forty times that of the tetrapositively charged tetrapyridylporphin [97]. Cu is incorporated about 20,000 times as rapidly into protoporphyrin dimethyl ester when solubilized in the negative detergent sodium dodecyl sulfate than in the positively charged cetyltrimethylammonium bromide [90]. The activation energy of the negative detergent reaction was 7 kcal/mole less than for the positive detergent.

Several groups [94, 95] have shown that the relative incorporation rates in aqueous solution depend on the metal ion in the approximate order $Cu^{2+} > Zn^{2+} > Co^{2+}, Fe^{2+}, Mn^{2+} > Mg^{2+}, Ni^{2+} \gg Al^{3+}, Fe^{3+}, Cr^{3+}$. These relative rates roughly parallel the rates of water exchange by aquo ions [94] and it has been suggested that the slow metal–porphyrin reactions compared to those of other ligand types arise from the necessity of removing more than one ligand at a time, bound to the central cation before metal incorporation [86]. Certain inner orbital chelating agents have been found to both facilitate or inhibit the rates of Cu incorporation [99]. An explanation based on charge delocalization on the cation, and consequent loosening of the remaining coordination sphere, has been advanced.

Brisbin and Balahura [100] have shown that when Mn^{2+} is mixed with the dication of hematoporphyrin in glacial acetic acid, a monocation spectrum is rapidly produced. Fe^{3+} and Co^{2+} acetates also produced this species, but Zn^{2+} and Cu^{2+} showed no such intermediate. The porphyrin product of the Mn^{II} reaction was $Mn^{III}P$, produced by a rate law first order in Mn^{II} and PH_3^+. The reaction was formulated as

$$PH_3^+ + Mn^{2+} \rightleftharpoons Mn^{III}P + 2\,H^+ + \tfrac{1}{2}\,H_2$$

Kingham and Brisbin [144] have shown that the rates of first row transition metal ion incorporation into hematoporphyrin in glacial acetic acid parallel the changes in crystal field stabilization energy for an S_N2 (six to seven coordinate) process. Along similar lines, the rate law for the insertion of Zn and Cd into porphyrins and *N*-methylporphyrins was the same, with the rates about 10^5 faster in the latter case. Neither basicity nor statistical factors could explain this difference, which was ascribed to the inherent non-planarity of *N*-methylporphyrins which must feature metal ion attack from only one side [145].

H. STABILITY OF METAL IONS IN METALLOPORPHYRINS

Various methods have been used to probe the "stability" of metal ions in metalloporphyrins. Among them are acid-catalyzed dissociation reactions of the form

$$MP + 2\,H^+ \rightleftharpoons PH_2 + M^{2+}$$

Qualitative studies [6] have shown that water dissociates most alkali metal, Ca, Be, Hg or Pb chelates, dilute acids dissociate Zn, Cd and Mg complexes whereas concentrated sulfuric acid or methanesulphonic acid [101] demetallate Cu, Ni, Co, and trivalent Fe and Mn species. Lower acidities are required to dissociate metal ions coordinated to more basic porphyrins [102].

In sulfuric acid–acetic acid mixtures, the rates of metal ion displacements were found to be [103] Co > Ni < Cu < Zn. The dissociation of Cu etioporphyrin in this medium was shown to follow the rate law

$$-\mathrm{d}[\mathrm{CuP}]/\mathrm{d}t = k[\mathrm{CuP}]^2\,[h_0]^4$$

suggesting the mechanism

$$\mathrm{CuP} + 2\,\mathrm{H}^+ \rightleftharpoons \mathrm{CuP}\cdot 2\,\mathrm{H}^+$$

$$2\,\mathrm{CuP}\cdot 2\,\mathrm{H}^+ \rightarrow \text{products}$$

The experimental methods have been questioned several times [104,105].

Snellgrove and Plane [105] have studied the kinetics of a MgP displacement in methanol containing perchloric acid, pyridine and water. The observed rate law was

$$-\mathrm{d}[\mathrm{MgP}]/\mathrm{d}t = [\mathrm{MgP}]\,\{k_1[\mathrm{H}^+]^3/(\rho_1 + (\mathrm{H}^+)) + k_2[\mathrm{Py}]\,[\mathrm{H}^+]^3/(\rho_2 + [\mathrm{H}^+]) + k_3[\mathrm{Py}]\,[\mathrm{H}_2\mathrm{O}]\,[\mathrm{H}^+]^2\}$$

for a given step, the mechanism was

$$\mathrm{MgP} + 2\,\mathrm{H}^+ + \mathrm{X}^- \xrightleftharpoons[k_{nr}]{K_1 \ldots K_{n-1} k_{nf}} [\mathrm{X{-}MgPH_2}]$$

$$[\mathrm{X{-}MgPH_2}] + \mathrm{H}^+ \xrightarrow{k_{n+1}} \text{products}$$

In brief, a number of protonated or ligated species preceed the final rate determining step which will either be a third protonation, or the step prior to this at high acidities. The protonations and ligations facilitate one another such that "the bonding requirements of both the magnesium ion and the porphyrin nitrogens are met as the magnesium–nitrogen bonds are progressively weakened and the magnesium ion is removed from the porphyrin plane".

The dissociation of Mn^{II} from hematoporphyrin [106] in water–ethanol mixtures was first order in MnP. The reaction was first order in (H^+) at low and high acidities, and of an order higher than first at intermediate pH's.

The only acid-catalyzed solvolysis reaction of metal porphyrins studied in aqueous solution was the dissociation of Zn from the water soluble meso-tetra(4-*N*-methylpyridyl)-porphin [97,107]. The reactions were first order in ZnP and at acid concentrations of 1.0 *N*, the relative rates were

$$\begin{array}{ccccccccc} HI & < & H_2SO_4 & < & HNO_3 & < & HBr & < & HCl \\ 1 & & 8 & & 85 & & 186 & & 675 \end{array}$$

The rate law was

$$-d[ZnP]/dt = k_s[H^+]^2[X^-]^2$$

with k_s in the order $Cl^- > Br^- > I^-$. For NO_3^-, the rate law was squared in $[H^+]$, but first order in $[NO_3^-]$. In HCl–methanol [108], the rates of Zn ion replacement from zinc porphyrins were faster the higher the porphyrin basicity. The rate law, $R = k[ZnP][HCl]^x/(\rho + [HCl])$ was found with porphyrins ($x = 3$) and *N*-methylporphyrins ($x = 2$). The *N*-methyl derivatives have three rather than four coordination with respect to the porphyrin. One or two protons were viewed as attacking the lone pairs on opposite pyrrole nitrogens bending these pyrrole planes downward, with the other two moving upward, thus lifting the coordinated Zn from the now formally neutral porphyrin. In a concerted fashion one or two halides occupy the vacated coordination positions on the zinc ion. The final one proton attack in either case makes the metal ion one coordinate with respect to the porphyrin, leading to solvolysis. No large charge separation (P^{2-} from Zn^{2+}) need occur.

Eisner and Harding [109] have demonstrated that metalloporphyrins can be ranked in stability with respect to the number of equivalents of lithium in ethylenediamine required for the discharge of the metal ion. The relative order was Pt > Pd > VO > Ni > Co > Cu > Sn^{IV}, Fe^{II}. The mechanism was unclear and Fleischer [9] has noted that the porphyrin nitrogen–metal ion bond lengths show a correlation with the tendency toward dissociation.

Dempsey and coworkers [4] have estimated an equilibrium constant $\log K_s$ of 29 for the following reaction involving mesoporphyrin:

$$Zn^{2+} + P^{2-} \rightleftharpoons ZnP$$

The high value shows the extreme stability of the four coordinate chelates compared with less rigid ligands. Such equilibria have been little studied because the requisite constants (P^{2-}–PH_2) are not well known, and the approach to equilibrium is often slow, or too far to one side to determine.

Corwin and Wei [102] have measured the equilibrium between porphyrins and chlorins at 100°K in phenol.

$$PH_2 + Mg(OC_6H_5)_2 \overset{K}{\rightleftharpoons} MgP + 2\,C_6H_5OH$$

The porphyrins were found more stable than the less basic chlorins, and etioporphyrin replaces Mg from its corresponding chlorin complex in refluxing acetic acid [110].

Barnes and Dorough [111] have investigated the replacement of one divalent ion for another coordinated in a meso-tetraphenylporphin chelate,

$$M_a + M_bP = M_aP + M_b$$

No measurable equilibrium was observed, and the relative displacement order was $Cu > Zn > Hg > Pb > Li_2 > Na_2 > K_2$ or small divalent > large divalent > alkali ions. Similar results have been found by other workers [6].

Kinetic studies have indicated a possible multiplicity of mechanisms for such exchanges [112]. For example in the Cu–ZnP system, the rate law in refluxing pyridine was

$$-d[ZnP]/dt = k[ZnP][Cu]/(k' + [Zn])$$

This is consistent with several mechanisms involving unstable intermediates; for example

$$ZnP + Cu^{2+} \rightleftharpoons [CuP^*] + Zn^{2+}$$

$$[CuP^*] \rightarrow \text{products}$$

or

$$ZnP \rightleftharpoons Zn^{2+} + P^{2-}$$

$$Cu^{2+} + P^{2-} \rightleftharpoons [CuP^*]$$

$$Zn^{2+} + [CuP^*] \rightarrow \text{product}$$

The Zn–CdP and Zn-HgP reactions were first order in metal ion and porphyrin, while the Zn–Pb reaction was second order in Zn. Free base intermediates were excluded, and the Zn–PbP reaction was catalyzed by Hg^{II}.

Under normal conditions, most metalloporphyrins are fairly inert to exchange by the corresponding isotope. Little exchange has been found with Mg chlorophyll *a* or *b* [113], Fe^{III} porphyrins [114], Cu pheophytin and Co^{II} mesoporphyrin [115]. Sodium ions rapidly exchange with disodium porphyrins [111], and Mg exchanges with chlorophyll derivatives in a petroleum ether soluble plant material extract [116]. Fe exchanges with ferric deuteroporphyrins in resorcinol melts [6].

From a consideration of various "stability" criteria, Phillips [3] has advanced the following order $Pt^{II} > Pd^{II} > Ni^{II} > Co^{II} > Ag^{II} > Cu^{II} > Zn^{II} > Mg^{II} > Cd^{II} > Sn^{II} > Li_2 > Na_2 > Ba^{II} > K_2 > Ag^{I}_{2}$. The more "stable" the metal ion, the higher the net positive charge on the porphyrin ring. Thus the one electron oxidation potentials of metalloporphyrins[117] increase with the metal ion stability, and reduction potentials follow the opposite trend.

I. SUBSTITUTION AND ELECTRON TRANSFER REACTIONS

Fleischer and coworkers [118] have studied the kinetics of the nucleophilic substitution reactions of diaquo Fe^{III} and Co^{III} hematoporphyrin with CN^- and SCN^-, of the form

$$MP(OH_2)_2 + 2\,X^- \rightleftharpoons MPX_2 + 2\,H_2O$$

The observed rates were always first order in porphyrins with the Fe^{III} system following a linear rate dependence and the Co^{III} reactions showing a leveling effect with X^-. An S_N1 limiting mechanism was assumed for all of the reactions:

$$MP(OH_2)_2 \rightleftharpoons MP(OH_2) + H_2O$$

$$MP(OH_2) + X \rightarrow MP(OH_2)X \quad \text{slow}$$

$$MP(OH_2)X + X \rightarrow MPX_2 + H_2O \quad \text{fast}$$

The cobalt substitution reactions were rapid compared to most d^6 systems, and electron delocalization into the porphyrin molecule was suggested. It was noted than an ion-pair substitution mechanism could not be excluded on kinetic grounds.

Ethanol was used to monomerize Fe^{III} protoporphyrin, and temperature jump and NMR line broadening studies were used to elucidate the mechanism of imidazole addition to hemin. From the NMR work [119], the rate constants for the dissociation of ethanol from hydroxy-ethanol hemin was 2×10^6 sec^{-1}, and of water from hydroxy-aquo hemin was 6×10^5 sec^{-1}. From T-jump data [120], the rate constants for the reactions of hydroxy-ethanol hemin with imidazole (3×10^4 $M^{-1}sec^{-1}$) and the imidazonium ion (4×10^6 M^{-1} sec^{-1}) were determined. The rates were inconsistent with a limiting S_N1 formulation, and were suggested to follow an ion-pair process

$$OH{-}FeP{-}Et + ImH^+ \rightleftharpoons OH{-}FeP{-}Et(ImH^+) \quad K_{ip}$$

$$OH{-}FeP{-}Et(ImH^+) \rightarrow OH{-}FeP{-}Im + H^+ + Et$$

The faster rate of the imidazonium reaction was attributed to a larger ion-pair formation constant (ca. 3) as compared to abont 0.02 for imidazole.

The kinetics of the one electron oxidations of Cr^{II}, V^{II}, Eu^{II}, and $Cr(bipy)_3^{2+}$ with Mn^{III} and Fe^{III} meso-tetrapyridylporphins in the presence of halides have been studied by stopped-flow techniques [121].

$$Mn^{III}P + Red \xrightarrow{X} M^{II}P + Ox$$

The reactions were halide catalyzed in the order $SCN^- > Cl^- > Br^- > I^-$, and showed rate laws of the form

$$-d[M^{III}P]/dt = [Red]\,[M^{III}P] \quad (k_1 + k_2X)$$

The iron reactions were more susceptible to halide catalysis than those of manganese. The fact that Cl^- was incorporated into the product chromium species indicated substitution of this ligand into the chromous coordination shell before electron transfer, but the lability of both Fe^{III} and Mn^{III} porphyrins precluded a definite mechanistic assignment. The reactivity pattern appeared to favor the V^{II} and $Cr(bipy)_3^{2+}$ as outer sphere reductants and Cr^{II} as an inner sphere reactant. In parallel with their more stable oxidized forms [5], the metalloporphyrin electron transfer reactions were slower than their aquo ion counterparts.

Castro and Davis [122] have shown that the reduction of Fe^{III} octaethylporphin by Fe^0 in 1:1 *N*-methylpyrolidine–$CH_3CO_2D(T)$ and subsequent reoxidation by O_2 or H_2O_2 leads to deuterium or tritium incorporation at the meso positions of the porphyrin. A mechanism featuring hydrogen atom attack at the meso positions, with the subsequent radical reducing the Fe^{III} was postulated. It was noted that such a mechanism could explain electron transfer in hemoproteins where the axial positions of the porphyrin were fully substituted.

The kinetics of oxidation of dipyridine Fe^{II} porphyrins by molecular oxygen in aqueous and ethanol–benzene solutions were reported to follow a rate law [123]

$$-d[\text{heme}]/dt = 4(k_a/[\text{Py}] + k_b)[O_2][\text{heme}]$$

consistent with the mechanism

$$\begin{tikzcd} O_2 + \text{Py–FeP–Py} \arrow[r, phantom, "\rightleftharpoons"] \arrow[dr, "k_b"'] & \text{Py} + O_2\text{–FeP–Py} \arrow[d, "k_a"] \\ & \text{products} \end{tikzcd}$$

The oxidation thus proceeds by a direct outer sphere (k_b) pathway, and an inner-sphere pathway with the formation of an "oxyheme". It was shown that the oxidation rates decreased with solvent polarity, in accord with the hypothesis is that oxyheme decomposes into O_2^- (or HO_2) and $Fe^{III}P$.

Cohen and Caughey [124], however, found more complicated rate behavior in benzene–pyridine solvents. Their proposed mechanism was of the form

$$\text{Py–Fe}^{II}\text{P–Py} \rightleftharpoons [\text{Py–Fe}^{II}\text{P}] + \text{Py}$$

$$2[\text{Py–Fe}^{II}\text{P}] + O_2 \rightleftharpoons [\text{Py–FeP–}O_2\text{–FeP–Py}]$$

$$[\text{Py–FeP–}O_2\text{–FeP–Py}] + H_2O \rightarrow 2\,\text{Fe}^{III}\text{POH} + H_2O_2 + 2\,\text{Py}$$

In contrast to the previous study in water, they found no evidence for an outer-sphere reaction. Their mechanism favors the coordination of one O_2 to two ferrous porphyrins before electron transfer, and the necessity for two reducing equivalents at the reaction site.

Along these lines, Corwin and coworkers [125,126] have shown the reversible oxygenation of biimidazole and bipyridine complexes of mesohemes and protohemes in the solid state, and Wang [127] has described several novel model hemoglobin and cytochrome oxidase systems.

Solvents above a dielectric constant [84] of ca. 12 and unsaturated hydrocarbons [85] are found to cause the oxidation of Co^{II} porphyrins to Co^{III}. For the solvent induced oxidations, the process is reversible upon removal of the solvent, whereas with olefins, the porphyrin is decomposed. *Cis*- to *trans*-2-butene isomerization and spectral shifts indicated π bonding between the metal ion and hydrocarbon. Such bonding facilitates the formation of octahedral coordination by the Co^{II}, which is then unstable with respect to Co^{III}. The induced oxidations of Fe^{II} by olefins, however, have been ascribed to peroxide impurities [128]. The reactions of alkyl halides, quinones, nitro and nitroso compounds by ferrous porphyrins have also been described.

ACKNOWLEDGEMENT

We thank the Graduate School at Howard University and the U.S. Atomic Energy Commission for support.

REFERENCES

1 H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Akademische Verlagsgesellschaft, Leipzig, 1937, Vol. 2, Part 1.
2 R. Lemberg and J.W. Legge, *Haematin Compounds and Bile Pigments*, Interscience, New York, 1949.
3 J.N. Phillips, *Rev. Pure Appl. Chem.*, 10 (1960) 35.
4 J.E.Falk, R. Lemberg and R.K. Morton (Eds.), *Haematin Enzymes*, Pergamon, London, 1961.
5 J.E.Falk and J.N. Phillips, in *Chelating Agents and Metal Chelates*, F.P.Dwyer and D.P. Mellor (Eds.), Academic Press, New York, 1964, p. 442.
6. J.E. Falk, *Porphyrins and Metalloporphyrins*, Elsevier, Amsterdam, 1964.
7 J.N. Phillips, in *Comprehensive Biochemistry*, M. Florkin and H.E.Stolz (Eds.), Elsevier, Amsterdam, 1963, Vol. 9, p. 34.
8 J.L.Hoard, in *The Chemistry of Hemes and Hemoproteins*, B. Chance, R.W. Estbrook and T. Yonetani (Eds.), Academic Press, New York, 1966.
9 E.B. Fleischer, *Accounts Chem. Res.*, 3 (1970) 105.
10 H.H.Inhoffen, *Rev. Pure Appl. Chem.*, 17 (1968) 443.
11 A. Adler, F.R. Longo, J.D. Finarelli, J. Goldmacher, J. Assour and L. Korsakoff, *J. Org. Chem.*, 32 (1967) 476.
12 F.R. Longo, M.G. Finarelli and J.B. Kim, *J. Heterocycl. Chem.*, 6 (1969) 927.
13 E.B. Fleischer, *Inorg. Chem.*, 1 (1962) 493.
14 H.W. Whitlock and R. Hanaver, *J. Org. Chem.*, 33 (1968) 2169.
15 W.S. Caughey, J.O. Alben, W.Y. Fujimoto and J.L. York, *J. Org. Chem.*, 31 (1966) 2631.
16 W.S. Caughey, W.Y. Fujimoto and B.P. Johnson, *Biochemistry*, 5 (1966) 3830.
17 R.N. Harris, A.W. Johnson and I.T. Kay, *Quart. Rev.*, 20 (1966) 211.
18 W.H. McEwan, *J. Amer. Chem. Soc.*, 68 (1946) 711.
19 R.C. Ellingson and A.H. Corwin, *J. Amer. Chem. Soc.*, 68 (1946) 1112.
20 G.R. Dearden and A.H. Jackson, *Chem. Commun.*, (1970) 205.
21 M.J. Broadhust, R. Grigg and G. Shelton, *Chem. Commun.*, (1970) 231.
22 L.K. Gottwald and E.F. Ullman, *Tetrahedron Lett.*, 36 (1969) 3071.
23 A. Neuberger and J.J. Scott, *Proc. Roy. Soc. (London), Ser. A*, 213 (1952) 307.
24 P. Hambright and E.B. Fleischer, *Inorg. Chem.*, 9 (1970) 1757.
25 J.N. Phillips, in *Current Trends in Heterocyclic Chemistry*, A. Albert, G.M. Badger and C.W. Shopper (Eds.), Butterworth, London, 1965, p. 30.
26 B.F. Burnham and J.J. Zuckerman, *J. Amer. Chem. Soc.*, 90 (1970) 1547.

27 E.B. Fleischer and A.L. Stone, *J. Amer. Chem. Soc.*, 90 (1968) 2735.
28 E.B. Fleischer and L. Webb, *J. Phys. Chem.*, 67 (1963) 1131.
29 A. Treibs, *Liebigs Ann. Chem.*, 728 (1969) 115.
30 P. Rothermund and A.R. Menotti, *J. Amer. Chem. Soc.*, 70 (1948) 1808.
31 G.D. Dorough, C. Miller and F.M. Huennekens, *J. Amer. Chem. Soc.*, 74 (1952) 3974.
32 J.O. Alben, W.H. Fuchsman, C.A. Beaudreau and W.S. Caughey, *Biochemistry*, 7 (1968) 624.
33 N. Sadasivan, H.I. Eberspaecher, W.H. Fuchsman and W.S. Caughey, *Biochemistry*, 8 (1969) 534.
34 P.E. Wei, A.H. Corwin and R. Arellano, *J. Org. Chem.*, 27 (1962) 3344.
35 E.B. Fleischer and A. Laszlo, *Inorg. Nucl. Chem. Lett.*, 5 (1969) 373.
36 L.J. Boucher, *J. Amer. Chem. Soc.*, 90 (1968) 6640.
37 M. Calvin, *Rev. Pure Appl. Chem.*, 15 (1965).
38 B.D. Boylan and M. Calvin, *J. Amer. Chem. Soc.*, 89 (1967) 5472.
39 A.R. Kane, R.G. Yalman and M.E. Kenney, *Inorg. Chem.*, 7 (1968) 2588.
40 L.J. Boucher and J.J. Katz, *J. Amer. Chem. Soc.*, 89 (1967) 4073.
41 N. Sadasivan and E.B. Fleischer, *J. Inorg. Nucl. Chem.*, 30 (1968) 591.
42 E.B. Fleischer and D. Lavallee, *J. Amer. Chem. Soc.*, 89 (1967) 7132.
43 M. Tsutsui, R.A. Velapoldi, K. Suzuki, F. Vohwinkel, M. Ichikawa and T. Koyano, *J. Amer. Chem. Soc.*, 91 (1969) 6262.
44 A.B.P. Lever, *Advan. Inorg. Chem. Radiochem.*, 7 (1965) 27.
45 (a) L. Vogt, A. Zalkin and D. Templeton, *Inorg. Chem.*, 6 (1967) 1725;
(b) J.A. Elvidge and A.B.P. Lever, *Proc. Chem. Soc.*, (1959) 195.
46 E.B. Fleischer, Lecture at Howard University, 1970.
47 E.B. Fleischer and T.S. Srivastava, *J. Amer. Chem. Soc.*, 91 (1969) 2403.
48 I.A. Cohen, *J. Amer. Chem. Soc.*, 91 (1969) 1980.
49 C.B. Storm, *J. Amer. Chem. Soc.*, 92 (1970) 1423.
50 M.F. Reich and I.A. Cohen, *J. Inorg. Nucl. Chem.*, 32 (1970) 343.
51 N.J. Gogan and Z.U. Siddiqui, *Chem. Commun.*, (1970) 284.
52 G.W. Hodgson, E. Peterson, K.A. Kvenvolden, E. Bunnenberg, B. Haldern and C. Ponnamperuma, *Science*, 30 (1970) 763.
53 D.A. Clarke, D. Dolphin, R.G. Rigg, A.W. Johnson and H.A. Pinnock, *J. Chem. Soc. (C)*, (1968) 881.
54 E.W. Baker, Lecture at Howard University, 1970.
55 B. Burnham, *J. Chromatogr.*, 41 (1969) 394.
56 F.E. Senftle and W.P. Hambright, in: *Biological Effects of Magnetic Fields*, M. Barnothy (Ed.), Plenum Press, N.Y., 1969, Vol. 2, p. 261.
57 W.P. Hambright, A.N. Thorpe and C.C. Alexander, *J. Inorg. Nucl. Chem.*, 30 (1968) 3139.
58 R.J. Abraham and P.F. Swinton, *J. Chem. Soc. (B)*, (1969) 903.
59 B.D. McLees and W.S. Caughey, *Biochemistry*, 7 (1968) 642.
60 R. Havemann, W. Haberditzl and K.H. Mader, *Z. Phys. Chem.*, 218 (1961) 71.
61 H.A.O. Hill and K.G. M rallee, *Chem. Commun.*, (1970) 266.
62 K. Wuthrich, R.G. Schulman, R.J. Wyluda and W.S. Caughey, *Proc. Natl. Acad. Sci., U.S.*, 62 (1969) 636.
63 W.S. Caughey and L.F. Johnson, *Chem. Commun.*, (1969) 1362.
64 S. Sullivan, P. Hambright, B.J. Evans, A. Thorpe and J. Weaver, *Arch. Biochem. Biophys.*, 137 (1970) 51.
65 C. Maricondi, W. Swift and D.K. Straub, *J. Amer. Chem. Soc.*, 91 (1969) 5205.
66 P.L. Richards, W.S. Caughey, H. Eberspaecher, G. Feher and M. Malley, *J. Chem. Phys.*, 47 (1967) 1187.
67 M. Kotani, *Progr. Theor. Phys. Suppl.*, 17 (1961) 4.
68 T.H. Moss, A.J. Bearden and W.S. Caughey, *J. Chem. Phys.*, 51 (1969) 2624.
69 J.F. Boas, J.R. Pilbrow and T.D. Smith, *J. Chem. Soc. (A)*, (1969) 721.
70 D.A. Doughty and C.W. Dwiggins, Jr., *J. Phys. Chem.*, 73 (1969) 423.
71 T.M. Bednarski and J. Jordan, *J. Amer. Chem. Soc.*, 89 (1967) 1552.
72 J.G. Montalvo, Jr. and D.G. Davis, *J. Electroanal. Chem.*, 23 (1969) 164.

73 W.S. Caughey, H. Eberspaecher, W.H. Fuchsman and S. McCoy, *Ann. N.Y. Acad. Sci.*, (1969) 722.
74 D. Mauzerall, *Biochemistry*, 4 (1965) 1801.
75 A.C. Mackly and A. Akeson, *Acta Chem. Scand.*, 12 (1958) 1259.
76 C.H. Kirksey and P. Hambright, *Inorg. Chem.*, 9 (1970) 958.
77 R. Lee and P. Hambright, *J. Inorg. Nucl. Chem.*, 32 (1970) 477.
78 A. Yamamoto, L.K. Phillips and M. Calvin, *Inorg. Chem.*, 7 (1968) 847.
79 J.E. Falk, J.N. Phillips and E.A. Magnusson, *Nature*, 212 (1966) 1531.
80 J.H. Wang, A. Nakahara and E.B. Fleischer, *J. Amer. Chem. Soc.*, 80 (1958) 1109.
81 J.O. Alben and W.S. Caughey, *Biochemistry*, 7 (1968) 175.
82 C.B. Storm, A.H. Corwin, R.R. Arellano, M. Martz and R. Weintraub, *J. Amer. Chem. Soc.*, 88 (1966) 2525.
83 C.H. Kirksey, P. Hambright and C.B. Storm, *Inorg. Chem.*, 8 (1969) 2141.
84 D.G. Whitten, E.W. Baker and A.H. Corwin, *J. Amer. Chem. Soc.*, 28 (1963) 2363.
85 M. Tsutsui, R.A. Velapoldi, L. Hoffman, K. Sozuki and A. Ferrari, *J. Amer. Chem. Soc.*, 91 (1969) 3337.
86 R.J. Kassner and J.H. Wang, *J. Amer. Chem. Soc.*, 88 (1966) 5170.
87 J. Weaver and P. Hambright, *Inorg. Chem.*, 8 (1969) 167.
88 D.K. Cabiness and D.W. Margerum, *J. Amer. Chem. Soc.*, 92 (1970) 2151.
89 R. Yalman, R. Overton and P. Hambright, *144th ACS Meeting, New York*, 1963.
90 M.B. Lowe and J.N. Phillips, *Science*, 190 (1961) 262.
91 E.B. Fleischer and J.H. Wang, *J. Amer. Chem. Soc.*, 82 (1960) 3498.
92 E.B. Fleischer, E.I. Choi, P. Hambright and A. Stone, *Inorg. Chem.*, 3 (1964) 1284.
93 P. Hambright, *J. Inorg. Nucl. Chem.*, 32 (1970) 2449.
94 E.I. Choi, and E.B. Fleischer, Inorg. Chem., 2 (1963) 94.
95 T.P. Stein and R.A. Plane, *J. Amer. Chem. Soc.*, 91 (1969) 607.
96 S.J. Baum and R.A. Plane, *J. Amer. Chem. Soc.*, 88 (1966) 910.
97 P. Hambright and E.B. Fleischer, *Inorg. Chem.*, 9 (1970) 1757.
98 J.N. Phillips, *Enzymologia*, 32 (1968) 13.
99 M.B. Lowe and J.N. Phillips, *Science*, 194 (1962) 1058.
100 D.A. Brisbin and R.J. Balahura, *Can. J. Chem.*, 46 (1968) 3431.
101 G.W. Hodgson, E. Peterson and B.L. Baker, *Mikrochim. Acta*, (1969) 805.
102 A.H. Corwin and P.E. Wei, *J. Org. Chem.*, 27 (1962) 4285.
103 W.S. Caughey and A.W. Corwin, *J. Amer. Chem. Soc.*, 77 (1955) 1509.
104 B.D. Berezin, *Russ. J. Phys. Chem.*, 36 (1962) 258.
105 R.Snellgrove and R.A. Plane, *J. Amer. Chem. Soc.*, 90 (1968) 3185.
106 D.G. Davis and J.G. Montalvo, Jr., *Anal. Chem.*, 41 (1969) 1195.
107 B. Shah and P. Hambright, *J. Inorg. Nucl. Chem.*, 32 (1970) 3420.
108 B. Shears, B. Shan and P. Hambright, *J. Amer. Chem. Soc.*, 93 (1971) 776.
109 U. Eisner and M.J.C. Harding, *J. Chem. Soc.*, (1964) 4089.
110 A.H. Corwin and M.H. Melville, *J. Amer. Chem. Soc.*, 77 (1955) 2755.
111 J.W. Barnes and G.D. Dorough, *J. Amer. Chem. Soc.*, 72 (1950) 4045.
112 C. Grant and P. Hambright, *J. Amer. Chem. Soc.*, 91 (1969) 4195.
113 S. Rubin, A.W. Frenkel and M.D. Kamen, *J. Phys. Chem.*, 46 (1942) 710.
114 S. Rubin, A.W. Frenkel, M.B. Allen and P. Nahinsky, *J. Amer. Chem. Soc.*, 64 (1942) 2297.
115 N. Ashelford and D.P. Mellor, *Australian J. Sci. Res.*, 5A (1952) 784.
116 R.S. Becker and R.K. Sheline, *J. Chem. Phys.*, 21 (1953) 946.
117 J.H. Fuhrhod and D. Mauzerall, *J. Am. Chem. Soc.*, 91 (1969) 4174.
118 E.B. Fleischer, S. Jacobs and L. Mestichelli, *J. Amer. Chem. Soc.*, 90 (1968) 2527.
119 N.S. Angerman, B.B. Hasinoff, H.B. Dunford and R.B. Jordan, *Can. J. Chem.* 47 (1969) 3217.
120 B.B. Hasinoff, H.B. Dunford and D.G. Horne, *Can. J. Chem.*, 47 (1969) 3225.
121 P. Hambright and E.B. Fleischer, *Inorg. Chem.*, 4 (1965) 912.
122 C.E. Castro and H.F. Davis, *J. Amer. Chem. Soc.*, 91 (1969) 5405.
123 O. Kao and J. Wang, *Biochemistry*, 4 (1965) 621.

124 I.A. Cohen and W.S. Caughey, *Biochemistry*, 7 (1968) 636.
125 A.H. Corwin and S.D. Bruck, *J. Amer. Chem. Soc.*, 80 (1958) 4736.
126 A.H. Corwin and Z. Reyes, *J. Amer. Chem. Soc.*, 78 (1956) 2437.
127 J.H. Wang, *Accounts Chem. Res.*, 3 (1970) 90.
128 R.W. Wade, R. Havlin and C.E. Castro, *J. Amer. Chem. Soc.*, 91 (1969) 7530.
129 L. Pauling and C.D. Coryell, *Proc. Natl. Acad. Sci. U.S.*, 22 (1936) 159.
130 L.M. Epstein, D.K. Straub and C. Maricondi, *Inorg. Chem.*, 6 (1967) 1720.
131 G. Blauer and A. Ehrenberg, *Biochim. Biophys. Acta.*, 112 (1966) 496.
132 P.A. Loach and M. Calvin, *Biochemistry*, 2 (1963) 361.
133 F.R. Longo, J.D. Finarelli and E. Schmalzbach, *J. Phys. Chem.*, 74 (1970) 3296.
134 A.D. Adler, J.H. Green and M. Mautner, *Org. Mass Spectrom.*, 3 (1970) 955.
135 J.W. Buchler, private communication.
136 T.S. Srivastava and E.B. Fleischer, *J. Amer. Chem. Soc.*, 92 (1970) 5518.
137 A. Wolburg and J. Manassen, *Inorg. Chem.*, 9 (1970) 2365; *J. Amer. Chem. Soc.*, 92 (1970) 2983.
138 F.E. Dickson and L. Petrakis, *J. Phys. Chem.*, 74 (1970) 2850.
139 R.A. Das, R.F. Pasternack and R.A. Plane, *J. Amer. Chem. Soc.*, 92 (1970) 3312.
140 S.J. Cole, G.C. Curthoys and E.A. Magnusson, *J. Amer. Chem. Soc.*, 92 (1970) 2991.
141 L.J. Boucher and H.K. Garber, *Inorg. Chem.*, 9 (1970) 2644.
142 F.A. Walker, *J. Amer. Chem. Soc.*, 92 (1970) 4235.
143 B.M. Hoffman and D.H. Petering, *Chem. Eng. News*, Sept., (1970) p. 41.
144 D.J. Kingham and D.A. Brisbin, *Inorg. Chem.*, 9 (1970) 2034.
145 B. Shah, B. Shears and P. Hambright, *Inorg. Chem.*, 10 (1971) in press.