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A Ferrochelatase Transition-State Model. Rapid Incorporation of Copper(II) into Nonplanar Dodecaphenylporphyrin

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The synthesis of a nonplanar dodecaphenylporphyrin (H$_2$DPP) and kinetic studies on Cu(II) incorporation into H$_2$DPP are described. The metalation reaction of H$_2$DPP was found to be rapid in comparison with that of a planar porphyrin, tetraphenylporphyrin, by a factor of 6×10^5. Another striking characteristic of the reaction of H$_2$DPP is saturation kinetics with respect to the concentration of Cu(II), indicative of the formation of an intermediate. The results provide strong evidence in support of the view that porphyrin ring distortion plays a key role in the transition state of the catalytic functioning of ferrochelatase.

Introduction

Studies on porphyrin metalation are of considerable importance owing to the widespread occurrence of metalloporphyrins in biological systems.[1] The final step in the heme biosynthetic pathway is the incorporation of Fe(II) into protoporphyrin IX to form protoheme, which is catalyzed by ferrochelatase.[2,3] Dailey et al.[4] proposed a model for the catalytic functioning of the active site of ferrochelatase in which porphyrin ring distortion is involved as a key transition-state intermediate: the distortion is presumed to be caused by steric and electronic interactions with amino acid residues present in the active site to facilitate metalation. This mechanism well explains the strong inhibition of ferrochelatase catalysis observed with distorted *N*-methylporphyrins.[3] Cochran and Schultz[5] recently reported the generation of antibodies to a hapten that mimics a strained conformation of the substrate of ferrochelatase. An antibody elicited to a distorted *N*-methylporphyrin indeed catalyzed metal ion chelation by the planar porphyrin.

Chemical studies have suggested that the mechanism of porphyrin metalation involves an association of the porphyrin with the metal ion and subsequent deformation of the porphyrin.[1,6,7] Quite slow rates[8] of metal ion incorporation are attributed to the difficulty of conformational change of the rigid planar porphyrin core. We reasoned that if porphyrin ring distortion in fact plays a key role in the transition state of both the enzymatic and nonenzymatic reactions, the metalation of a nonplanar porphyrin

should be distinct in reaction rates from that of planar porphyrins.[9]

We report here the synthesis[10] and rapid Cu(II) incorporation of dodecaphenylporphyrin (H$_2$DPP). Spectroscopic[10,11] and
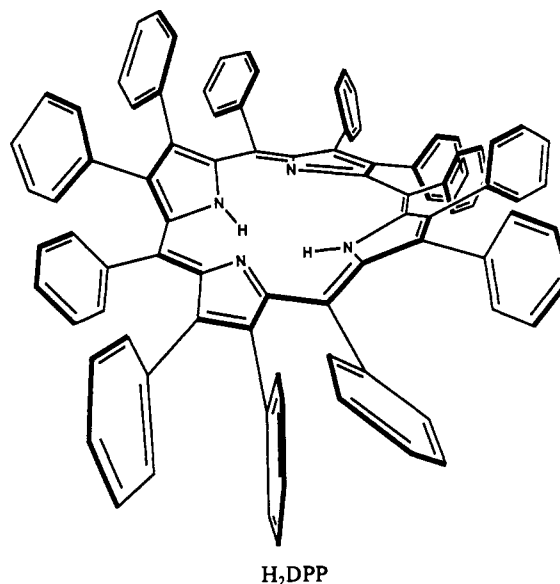
H$_2$DPP

preliminary X-ray studies[12,13] have shown that H$_2$DPP is permanently distorted to a saddlelike conformation in both solution and crystalline states.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a JEOL GSX-400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm with respect to internal tetramethylsilane. Ultraviolet and visible absorption spectra were recorded on a Hitachi 557 double-beam spectrophotometer equipped with thermostatic cell compartments.

Materials. All chemicals were of reagent grade. Dimethylformamide (DMF) was refluxed over BaO, distilled under reduced pressure, and stored over 4-Å molecular sieves. Alumina for column chromatography was Merck aluminum oxide 90 (activity II–III, 70–230 mesh). Silica gel for column chromatography was microbead silica gel, Grade 4B (neutral, 100–200 mesh), purchased from Fuji-Davison Chemical. 3,4-Di-

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phenylpyrrole was available from our previous work.[11] *meso*-Tetraphenylporphyrin (H$_2$TPP), (*meso*-tetraphenylporphinato)copper(II) (CuTPP), and bis(acetylacetonato)copper(II) (Cu(acac)$_2$) were prepared and purified by usual methods.

2,3,5,7,8,10,12,13,15,17,18,20-Dodecaphenylporphyrin, H$_2$DPP. A hot solution of 3,4-diphenylpyrrole (10.8 mmol, 2.37 g) in 60 mL of acetic acid was added to a refluxing solution of benzaldehyde (10.8 mmol, 1.15 g) in 100 mL of acetic acid. The solution rapidly turned purple, indicating formation of the porphyrinogen. The mixture was refluxed for 20 h, and the color of the solution gradually turned brown. 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) (8.1 mmol, 1.84 g) was added to the reaction mixture, and the solution was refluxed for additional 1 h. Evaporation of the solvent gave a residue, which was passed through a short dry column (silica gel–CHCl$_3$) to remove DDQ and the reduced hydroquinone. A dark-green band was collected, and the solvent was evaporated to dryness. The residue was purified by silica gel column chromatography. Elution with dichloromethane removed a red band, and subsequent elution with chloroform gave a large slow-moving green band of the acid dication form of H$_2$DPP. The green band was collected and evaporated to dryness. The residue was dissolved in dichloromethane (200 mL), and the mixture was treated with saturated NaOH solution (1 mL; stirred vigorously for 10 min). The organic solution was dried over anhydrous Na$_2$CO$_3$ and concentrated by evaporation. Heptane was added gradually, and the solution was left overnight. Purple needles were collected by filtration and washed with heptane (1.82 g, 1.49 mmol, 55% yield): ^{1}H NMR (CDCl$_3$) δ 6.64–6.80 (52 H, m, pyrr β-Ph and *meso*-Ph meta, para), 7.58 (8 H, d, *J* = 6.78 Hz, *meso*-Ph ortho); UV–vis (DMF) λ_{max} ($\epsilon \times 10^{-3}$, cm^{-1} M^{-1}) 479 (101), 571 (3.63), 645 (7.33), 754 nm (2.67). Anal. Calcd for C$_{92}$H$_{62}$N$_4$·H$_2$O: C, 89.00; H, 5.20; N, 4.51. Found: C, 88.70; H, 4.98; N, 4.65.

(2,3,5,7,8,10,12,13,15,17,18,20-Dodecaphenylporphinato)copper(II), CuDPP. To a DMF (30 mL) solution of H$_2$DPP (50 mg, 0.041 mmol) was added copper(II) acetate hydrate (50 mg, 0.25 mmol). The mixture was stirred at room temperature for 5 min. The UV–vis spectrum indicated no free base at this time. The mixture was added to 100 mL of water containing NaCl (5 g). The precipitate was collected by filtration and washed well with water. The resulting solid was air-dried and purified by alumina column chromatography (CHCl$_3$). A green band was collected and evaporated to dryness. Recrystallization from dichloromethane–heptane gave dark green crystals in quantitative yield: UV–vis (toluene) λ_{max} ($\epsilon \times 10^{-3}$, cm^{-1} M^{-1}) 448 (175), 580 (15.4), 623 nm (8.60). Anal. Calcd for C$_{92}$H$_{60}$N$_4$Cu: C, 85.99; H, 4.71; N, 4.36. Found: C, 86.02; H, 4.73; N, 4.35.

Repetitive Scan Measurements of the Reaction between H$_2$DPP and Cu(acac)$_2$. Since the reaction of H$_2$DPP with Cu(acac)$_2$ under kinetic pseudo-first-order conditions was very rapid, the repetitive scan measurements were done at low concentrations of both species. A 3.0-mL portion of H$_2$DPP stock solution (ca. 9.3 × 10^{-6} M in DMF) was placed in the cuvette. After the cuvette was equilibrated at 30 °C, 0.5 mL of Cu(acac)$_2$ stock solution (7.0 × 10^{-5} M in DMF) was pipetted into the cuvette. The reaction was monitored by a repetitive scan mode (5-min intervals) from 800 to 500 nm (Figure 1).

Kinetic Measurements of the Reaction between H$_2$DPP and Cu(acac)$_2$. All kinetic runs were followed by UV–vis spectrometry at a fixed wavelength (442 nm) in DMF solution at 30 °C. In a typical experiment, 3.0 mL of H$_2$DPP stock solution ((0.5–1.0) × 10^{-5} M in DMF) was placed in the cuvette. After the cuvette was equilibrated at 30 °C, 0.5 mL of Cu(acac)$_2$ stock solution (a known concentration in DMF) was pipetted into the cuvette. The reaction was followed by monitoring with time the appearance of the peak at 442 nm assigned to CuDPP.

Kinetic Measurements of the Reaction between H$_2$TPP and Cu(acac)$_2$. The reaction of H$_2$TPP with Cu(acac)$_2$ in DMF at 30 °C was too slow for the investigation of Cu(acac)$_2$ concentration dependence of the rate constants. Thus, we determined the rate constant at only one Cu(acac)$_2$ concentration. A 3.0-mL quantity of Cu(acac)$_2$ stock solution (8.42 × 10^{-3} M in DMF, almost saturated) was placed in the cuvette. After the cuvette was equilibrated at 30 °C, 0.5 mL of H$_2$TPP stock solution was pipetted into the cuvette. The reaction was followed by repetitive scans from 700 to 500 nm at 90-min intervals.

Results and Discussion

Synthesis of H$_2$DPP. Dodecaphenylporphyrin, H$_2$DPP, was synthesized by a modified method of Adler et al.[14] and Dolphin.[15] Condensation of 3,4-diphenylpyrrole and benzaldehyde in refluxing acetic acid for 20 h followed by oxidation with DDQ for 1 h gave
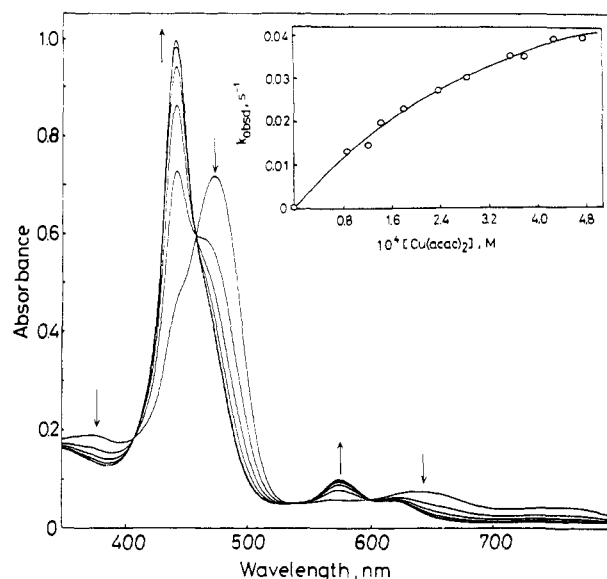
Figure 1. Repetitive scans at 5-min intervals for the reaction of H$_2$DPP (ca. 8 × 10^{-6} M) with Cu(acac)$_2$ (1.0 × 10^{-5} M) in DMF at 30 °C. Inset: Dependence of k_{obsd} upon [Cu(acac)$_2$]. The solid line is fitted to eq 4.

H$_2$DPP in 55% yield. The formation of H$_2$DPP was slow as compared with that of the hybrid porphyrins so far reported:[15,16] the desired porphyrin was not detected spectrophotometrically even after 3 h. Dolphin[15] and Evance et al.[16] reported that reactions of 3,4-dialkylpyrroles with benzaldehyde were rapid and complete within 30 min. In contrast to dialkyl groups, diaryl groups are presumed to hinder the autoxidation of intermediates such as the porphyrinogen and the porphodimethene derived from 3,4-diarylpyrrole. This agrees with our previous observations:[17] octaarylporphyrinogen and octaarylporphodimethene are unusually stable toward autoxidation. Octaarylporphyrins have been synthesized in high yields (70–86%) by DDQ oxidation of the porphyrinogen and the porphodimethene formed by cyclization of 3,4-diphenylpyrrole with formaldehyde. DDQ oxidation is effective to complete the porphyrin formation reaction involving 3,4-diphenylpyrrole as the starting material. The yield of H$_2$DPP obtained by our method is 55%, much higher compared with that obtained by the method of Lindsey et al.[18] In our hands, the yield obtained by the latter method was 3–5% (reported value 5.7%[10]).

Metalation Reaction. The reaction between H$_2$DPP and Cu(acac)$_2$ was examined spectrophotometrically in DMF solutions at 30 °C. Since the reaction of H$_2$DPP with Cu(acac)$_2$ was very rapid (vide infra), the spectral change shown in Figure 1 was measured under low concentrations of H$_2$DPP (=8 × 10^{-6} M) and Cu(acac)$_2$ (=1.0 × 10^{-5} M). The initial spectrum in Figure 1 is almost identical to that of the free base in DMF. Repetitive scanning from 800 to 350 nm revealed tight isosbestic points (407, 458, 520, and 600 nm).

Kinetics of Cu^{2+} Incorporation into H$_2$DPP. All kinetic studies were run under pseudo-first-order conditions ([H$_2$DPP] = (0.5–1) × 10^{-5} M and [Cu(acac)$_2$] = (0.8–4.8) × 10^{-4} M). In this range of the copper concentration, half-lives of H$_2$DPP were 15–60 s and reaction rates were determined by monitoring with time the absorbance of the CuDPP peak at 442 nm. The reaction of H$_2$DPP with Cu(acac)$_2$ followed pseudo-first-order kinetics up to 3 half-lives. The observed pseudo-first-order rate constant, k_{obsd}, was not directly proportional to Cu(acac)$_2$ concentration: with increasing Cu(acac)$_2$ concentration, the k_{obsd} value increases to reach ultimately a [Cu(acac)$_2$]-independent plateau (Figure 1: inset).

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Table I. Kinetic Data for the Cu(II) Incorporation Reaction[a] and pK_a Data[b] of H$_2$DPP and H$_2$TPP

porphyrin	k_1, s^{-1}	K, M^{-1}	k_{app}, M^{-1} s^{-1}	pK_3	pK_4
H$_2$DPP	0.079	2100	166	>13	>13
H$_2$TPP			0.00027	3.85	4.26

[a] Measured in DMF at 30 °C. [b] Determined by spectrophotometric titrations in aqueous 0.1 M sodium dodecyl sulfate micellar solutions at 25 °C. pK_3 and pK_4 refer to eqs 8 and 7, respectively.

The most reasonable kinetic scheme that fits the results involves an equilibrium between the reactants and an intermediate complex, H$_2$DPP···Cu^{2+}, prior to the CuDPP formation.

$$H_2DPP + Cu^{2+} \xrightleftharpoons{K} H_2DPP\cdots Cu^{2+} \quad (1)$$

$$H_2DPP\cdots Cu^{2+} \xrightarrow{k_1} CuDPP + 2H^+ \quad (2)$$

The kinetic scheme leads to the rate expressions

$$+d[CuDPP]/dt = -d[DPP]_{eq}/dt = k_{obsd}[DPP]_{eq} \quad (3)$$

$$k_{obsd} = k_1 K[Cu^{2+}]/(1 + K[Cu^{2+}]) \quad (4)$$

where [DPP]$_{eq}$ = [H$_2$DPP] + [H$_2$DPP···Cu^{2+}].

Tanaka and co-workers[19] have reported that the concentration dependence of the rate constants of the reaction of H$_2$TPP with Cu(ClO$_4$)$_2$ and Zn(ClO$_4$)$_2$ in DMF indicates a mechanism involving an additional step:

$$H_2DPP\cdots Cu^{2+} + Cu^{2+} \xrightarrow{k_2} CuDPP + Cu^{2+} + 2H^+ \quad (5)$$
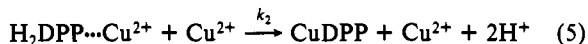
The rate expression involving eqs 2 and 5 is formulated as

$$k_{obsd} = \frac{(k_1 + k_2[Cu^{2+}])K[Cu^{2+}]}{1 + K[Cu^{2+}]} \quad (6)$$

which is, of course, reduced to eq 4 in the case where $k_1 \gg k_2[Cu^{2+}]$. On the other hand, as noted by Robinson and Hambright,[9] the same kinetic behavior as in eq 4 obtains if the complex H$_2$DPP···Cu^{2+} were viewed as a dead-end intermediate and if the reaction proceeded bimolecularly with the rate k'[H$_2$DPP][Cu^{2+}]. Steady-state kinetics alone will not distinguish between these two mechanisms, and we follow the previous workers[9,19] in postulating that the kinetically determined complex lies along the reaction pathway (eqs 1 and 2).

The rate expressions (eqs 3 and 4) adequately account for the observed saturation kinetics. The data plotted in the inset of Figure 1 were fitted to eq 4 with a nonlinear-least-squares program to give k_1 = 7.9 × 10^{-2} s^{-1} and K = 2.1 × 10^3 M^{-1}. Fitting to eq 6 gives $k_1 \gg k_2[Cu^{2+}]$; consequently, eq 5 need not be taken into consideration. The apparent rate constant k_{app} of CuP formation (P = porphyrin dianion), defined by d[CuP]/dt = k_{app}[H$_2$P]-[Cu^{2+}], therefore, is calculated as k_1K (=166 M^{-1} s^{-1}). The metalation reaction proceeds via the intermediate, which may be regarded as a kinetically detected sitting-atop (SAT) complex (k_1 path). The k_2 path (eq 5) in which the second metal ion should be inserted from the opposite side of the first metal ion in the SAT complex is neglected in the H$_2$DPP–Cu(acac)$_2$ system.

By contrast, in the H$_2$TPP–Cu(ClO$_4$)$_2$ system,[18] the k_2 path is kinetically favorable because the basicity of H$_2$TPP is increased by the distortion of the porphyrin ring. A similar phenomenon is observed for the protonation of H$_2$TPP (vide infra). As shown in Table I, the pK_4 value is larger than pK_3 value. The first protonation of planar H$_2$TPP deforms the resulting monocation species, causing the basicity to increase, and the second protonation occurs more easily. The metalation of the permanently distorted and highly basic H$_2$DPP does not require catalysis by the second metal ion. The kinetic data and the basicity of H$_2$DPP are given in Table I.

Kinetics of Cu^{2+} Incorporation into H$_2$TPP. The reaction of the planar porphyrin, H$_2$TPP, with Cu(acac)$_2$ under similar

Scheme I
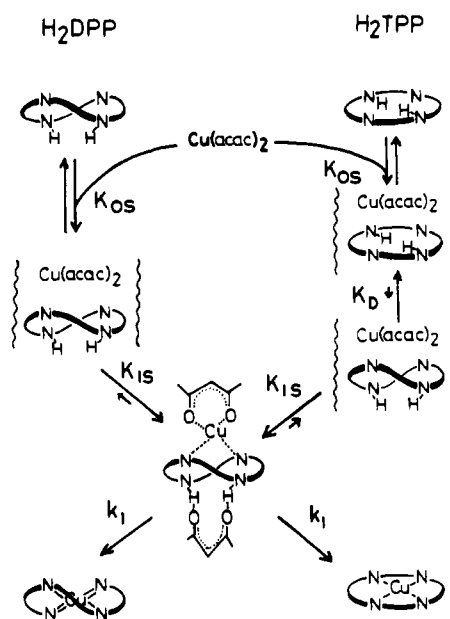
conditions is too slow for the precise kinetics to be investigated; the half-life is about 100 h at [Cu(acac)$_2$] = 7.22 × 10^{-3} M (k_{obsd} = 1.9 × 10^{-6} s^{-1}). Moreover, the reaction is light-sensitive and is accelerated even with room light. Although the precise kinetics was not elucidated, the apparent rate constant k_{app} defined above was calculated in order to roughly compare the magnitudes of the H$_2$TPP and H$_2$DPP systems. The obtained value is k_{app} = 0.00027 M^{-1} s^{-1} at [Cu^{2+}] = 7.22 × 10^{-3} M.

The kinetic data and the basicity of H$_2$TPP are compared with those of H$_2$DPP in Table I. The Cu(II) incorporation rate of the nonplanar porphyrin is enhanced in comparison with that of the planar porphyrin by a factor of 6 × 10^5.

Mechanism of Cu^{2+} Incorporation into H$_2$DPP and H$_2$TPP. The mechanisms of the Cu(II) incorporation reactions of H$_2$DPP and H$_2$TPP are compared in Scheme I. The mechanisms involve outer-sphere (K_{OS}) and inner-sphere (K_{IS}) associations of a metal ion with a porphyrin and deformation of a planar porphyrin (K_D). However, the deformation process is excluded for the metalation of permanently distorted H$_2$DPP. Thus, the experimentally observed equilibrium constant K for the H$_2$DPP system is equal to the product $K_{OS}K_{IS}$, whereas the K value for the H$_2$TPP system should be the product $K_{OS}K_DK_{IS}$. The saturation kinetics observed for the reaction of H$_2$DPP indicates that a metal ion and an H$_2$DPP molecule readily associate to form a SAT complex[6,7] ([H$_2$DPP]/[H$_2$DPP···Cu^{2+}]) = 1 at [Cu(acac)$_2$] = 4.8 × 10^{-4} M was calculated from the observed K value). It is noted that the initial spectrum shown in Figure 1 is essentially identical to that of the free base. The initial concentration of the intermediate complex was calculated to be [H$_2$DPP···Cu^{2+}] = 1.6 × 10^{-7} M with K = 2100 M^{-1} under the initial conditions ([H$_2$DPP]$_0$ = 0.8 × 10^{-5} M and [Cu(acac)$_2$]$_0$ = 1.0 × 10^{-5} M).

Scheme I is also supported by the thermodynamic data (Table I) on the acid dissociation for the porphyrins:

$$H_4P^{2+} \xrightleftharpoons{K_4} H_3P^+ + H^+ \quad (7)$$

$$H_3P^+ \xrightleftharpoons{K_3} H_2P + H^+ \quad (8)$$
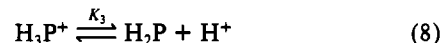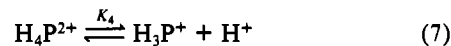
where H$_4$P^{2+} is the acid dication, H$_3$P$^+$ is the acid monocation, and H$_2$P is the free base of the porphyrin. A SAT complex is regarded as an acid dication analogue where two protons are replaced by a metal ion. It has been proposed that a SAT complex is deformed in a manner similar to that for the acid dication of H$_2$TPP.[20] H$_2$DPP is anticipated from its large pK_3 and pK_4 values (>13) to have high affinity for a metal ion. On the other hand,

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the acid dissociation constants K_3 and K_4 for H_2TPP are 10^9 times larger than those for H_2DPP; the formation of the SAT complex involving a deformation process seems to be thermodynamically unfavorable. The rapid metalation of H_2DPP is the result of high affinity for a metal ion due to nonplanarity of the porphyrin core.

Structures 1 and 2 are kinetically equivalent representations of the intermediate complex in the reaction of H_2DPP with Cu-

1   2
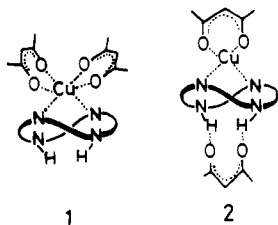
(acac)$_2$. In structure 1, acetylacetonato anions bisligate to Cu^{2+}. In structue 2, a single acetylacetonato anion serves as the ligand, while the other hydrogen-bonds to protons at the opposite side of Cu^{2+}. The metalation reaction proceeds only through the k_1 pathway, not through the k_2 pathway. One interpretation is that the SAT complex in the transition state of the reaction has structure 2. The k_2 pathway is blocked by an acac ligand attached to the "back side" of the porphyrin, the acac ligand being likely to serve as an efficient proton acceptor in the k_1 pathway.

Similar rate enhancement caused by porphyrin ring distortion has been observed for the metalation reactions of N-alkylporphyrins.[6a,7a,19] However, several differences should be pointed out: (1) no saturation kinetics has been observed for N-alkylporphyrin systems; (2) therefore, there is no direct evidence of a SAT complex as an intermediate; (3) products of H_2DPP reactions with divalent metal ions are neutral metalloporphyrins instead of the monocationic species formed in reactions of N-alkylporphyrins, which are gradually dealkylated in DMF; (4) in the case of an N-alkylporphyrin, the metal ion may attack only one side of the porphyrin ring owing to steric hindrance of the alkyl group at the nitrogen atom.

The porphyrin core of N-alkyl derivatives is forced to distort from planarity by the bulky central N-alkyl groups. On the other hand, steric crowding of the peripheral substituents causes H_2DPP to adopt a nonplanar conformation. Hence, H_2DPP is far more appropriate as a model for the ferrochelatase transition-state intermediate in which the porphyrin ring is distorted because of steric and electronic interactions with amino acid residues in the active site.

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Kinetics of the Reaction of Copper(II) with Cobalt(II) Sepulchrate: Catalysis by Chloride Ion and Imidazole

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The kinetics of the oxidation of cobalt(II) sepulchrate by aqueous copper(II) have been studied in the presence of chloride ion, imidazole, and acetonitrile at 25 °C. The reaction rate increases with increasing concentrations of chloride ion (0.05–0.2 M in 0.50 M $HClO_4$/$LiClO_4$) and imidazole (0.025–0.09 M at pH 6.5, in 0.15 M $LiClO_4$), but is unaffected by 0.4 M acetonitrile (0.50 M $HClO_4$/$LiClO_4$). The reaction of Cu^{2+}(aq) and Co(sep)$^{2+}$ is complicated by the rapid formation of copper metal, and it was necessary to use O_2 as a scavenger for Cu^+(aq) in order to determine the rate constant of 5.0 ± 0.25 M^{-1} s^{-1} (0.02 M $HClO_4$, 0.48 M $LiClO_4$, 25 °C). This value and earlier results for reductions of Ru(III) complexes by Cu^+(aq) give a self-exchange rate constant of 5×10^{-7} M^{-1} s^{-1} for $Cu^{2+/+}$(aq) from the Marcus cross relationship. The $Cu^{II}(Cl)_n$ complexes have rate constants of 1.6×10^3, 1.5×10^4, and 4.5×10^5 M^{-1} s^{-1} for $n = 1-3$. The change in reactivity can be accounted for in terms of Marcus theory by the increased driving force and reduced charge, with a self-exchange rate constant for the $Cu^{II/I}(Cl)_n$ species of 2×10^{-4} M^{-1} s^{-1}. The $Cu^{II}(Im)_n$ complexes show a much smaller change in reactivity (35, 70, and 120 M^{-1} s^{-1} for $n = 2-4$) and a smaller self-exchange rate constant of $\sim 1 \times 10^{-7}$ M^{-1} s^{-1}.

Introduction

It has been known for many years[1] that chloride ion catalyzes the oxidation of ascorbic acid by aqueous copper(II), and it has been determined recently[2] that the rate coefficient for the [Cl$^-$][Cu^{2+}][ascorbate] pathway is 1.5×10^3 times larger than that for the uncatalyzed pathway. Chloride catalysis also was observed by Yandell[3] for the reaction of aqueous copper(II) and ferrocytochrome c in the presence of dioxygen. Yandell interpreted the results in terms of Cu(II)–Cl$^-$ complexes, with specific rate constants for Cu^{2+}(aq), CuCl$^+$, and CuCl$_2$ of 5.7, 2.3×10^2, and 5.6×10^3 M^{-1} s^{-1}, respectively. The reactivity was ascribed, using Marcus theory,[4] to the increased driving force for the reaction because of the stronger complexation of Cu(I) by chloride ion. However, this interpretation predicts a Cu(II)/Cu(I) self-exchange rate constant of 5.2 M^{-1} s^{-1}, which is much higher than the current

estimate[5] of $\sim 2 \times 10^{-4}$ M^{-1} s^{-1}. If self-exchange rate changes are ignored, then the driving force effect predicts that CuCl$^+$ should be 15 times more reactive than Cu^{2+}(aq). This is consistent with the factor of 39 found with ferrocytochrome c, but not with the factor of 6.4×10^2 for an outer-sphere mechanism with CuCl$^+$ in the ascorbate system. However, the latter is complicated by the possible formation of an inner-sphere Cu^{II}–ascorbate complex, so that Marcus theory may not be applicable.

In order to clarify the role of added potential ligands on oxidations by copper(II), we have studied the oxidation of a well characterized outer-sphere reagent, Co(sep)$^{2+}$,[6,7] in aqueous solution at 25 °C. The three ligands studied have been chosen because of their known complexation properties.[8] Chloride ion and imidazole complex with both Cu(I) and Cu(II), but more strongly with the former. Acetonitrile does not appear to complex

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