in which the electron has been removed from either a metal d orbital or a porphyrin π_{MO}. The relative ordering of the levels depends on the extraplanar ligand. For acetonitrile or pyridine, metal d lies highest; for CO as the extraplanar ligand, porphyrin π_{MO} is highest. Undoubtedly an important factor contributing to the relative ordering is the strong effect of CO on metal $d-\pi$ levels by back-bonding. A large difference between CO and pyridine (or acetonitrile) in π back-bonding ability might be sufficient to depress the metal d orbitals of π symmetry below π_{MO} of the porphyrin and change the site of oxidation.

Recent pmr studies have shown that the second extraplanar coordination site in ruthenium(II) carbonyl porphyrins is unusually labile[27] even though the ruthenium ion is presumably squarely in the porphyrin plane.[28] Apparently, the CO group in the ruthenium complexes acts both to control the site of oxidation and it also exerts a strong trans labilizing effect.

The $E_{1/2}$ values for the second oxidation of the ruthenium porphyrins (Table I) do not show the large extraplanar ligand effects on $\Delta E_{1/2}$ values that were observed for the first oxidation. The nature of the oxidation products obtained at the second oxidation wave are clearly of interest since depending on the extraplanar ligand the site of oxidation could be at the ruthenium

ion giving Ru(III) (L = CO) or Ru(IV) (L = py or CH_3CN) or at the porphyrin giving Ru(II)(P^{2+}) (L = CO) or Ru(III)(P$^+$) (L = py or CH_3CN). Although the doubly oxidized complexes are stable in dichloromethane on the time scale of the cyclic voltammetry experiment (seconds), on longer time scales they are unstable and react, probably with solvent or solvent impurities, giving the singly oxidized complexes and uncharacterized decomposition products.

Carbon monoxide is well known for its ability to coordinate to hemoglobin as well as to other heme-type enzymes. Moreover, CO is known to stabilize the iron(II) state with respect to oxidation to iron(III) in porphyrin environments, and in this manner inhibits the actions of biological systems. For instance, Fe^{II}(heme)(CO)(py) is resistant to oxidation by molecular oxygen in solution.[29] It seems reasonable to expect that the effects of CO on the redox properties of spin-paired iron(II) porphyrins should be related to the effects observed here, in electronically similar ruthenium complexes.

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(28) J. J. Bonnet, S. S. Eaton, G. R. Eaton, R. H. Holm, and J. A. Ibers, *J. Amer. Chem. Soc.*, 95, 2141 (1973).
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Metal Ion Porphyrin Interactions. II. Evidence for the Nonexistence of Sitting Atop Complexes in Aqueous Solution[1]

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Abstract: *meso*-Tetrapyridylporphine (TPyP) has been postulated to form "sitting-atop" (SAT) complexes in aqueous solution. 1:1 adducts between metal ions and porphyrins which are presumed to be universal intermediates in metal ion incorporation. The completely water soluble and monomeric tetrakis(N-methylpyridyl)porphine (TMTPyP), which is similar to TPyP, has been reported to show no SAT properties. To clarify the SAT problem, a study of the kinetics of Cu^{2+} incorporation into TMTPyP was done at 26°, from pH 0.5 to 3.5, as a function of ionic strength (NaNO$_3$). The rate law was of the form: rate = k[Cu^{2+}][NO$_3^-$][TMTPyP]/(1 + (H$^+$)/K_3 + (H$^+$)^2/K_3K_4). From equilibrium pH studies, K_3 and K_4 are the monocation–free base and dication–monocation dissociation constants, which increase with an increase in ionic strength. The rate determining step involves Cu^{2+}, NO$_3^-$, and only the free base form of the porphyrin. The results indicate that SAT complexes do not exist in aqueous solution with TMTPyP or TPyP. The SAT phenomena previously observed with TPyP can be explained by (1) an unusual anion term in the rate law, (2) the strong increase in pK_3 and pK_4 upon increase in ionic strength, and (3) the lack of reactivity of mono- and dication forms toward metal ions. The fact that all porphyrins do not incorporate metal ions by a single mechanism is discussed.

Over the past 12 years, a considerable effort has been made to determine the mechanisms by which metal ions insert into porphyrin molecules to form metalloporphyrins.[2]

$$M^{2+} + PH_2 \longrightarrow MP + 2H^+ \quad (1)$$

A particularly attractive idea was that of "sitting-atop" complexes,[3] which were observable adducts of metal ions with free base (PH$_2$) porphyrins that form prior to metal ion incorporation. Evidence for SAT complexes has been presented in two types of systems. In methanol–chloroform mixtures, protoporphyrin dimethyl ester[3] and various transition metal ions pro-

(1) Part I concerns metal ion substitution and exchange reactions: H. Baker, P. Hambright, L. Wagner, and L. Ross, *Inorg. Chem.*, 12, 2200 (1973).
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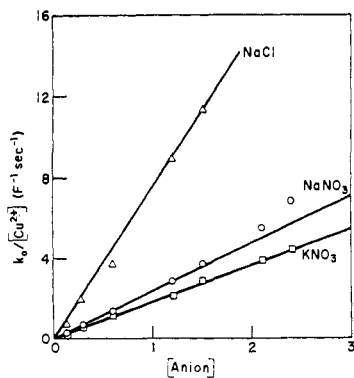(3) E. B. Fleischer and J. H. Wang, *J. Amer. Chem. Soc.*, 82, 3498 (1960).

Figure 1. Plot of $k_o/[Cu^{2+}]$ vs. anion for the reaction of Cu^{2+} with TMTPyP, 26°, pH 3.1, with various salts.

Figure 2. Plot of $k_o/([Cu^{2+}][NO_3^-])$ vs. pH for the reaction of Cu^{2+} with TMTPyP, at various ionic strengths, 26°. The solid theoretical curves were calculated from eq 2, with the data in Table I.

duced characteristic SAT visible spectra, which disappeared as the metalloporphyrin formed. It has been shown[4] in the case of Fe_2Cl_6, however, that the presumed spectra of SAT species arise from ion pair formation between the diprotonated diacid (H_4P^{2+}) and solvated anions $[Fe_2Cl_5(OEt)_2]^-$. This species is reasonable since a crystal structure is known[5] of a $[FeCl_4^-,Cl^-]$-diacid porphyrin salt.

The second SAT phenomenon was found[6] in aqueous solutions with meso-tetrapyridylporphine (TPyP). Over 20 metal ions and positive species $(NH_4^+, (C_2H_5)_4N^+)$ reacted with TPyP to produce 1:1 complexes, which had formation constants ranging from 1.5 for K^+ to 87 M^{-1} for Cu^{2+}. The kinetics of metal ion incorporation were shown to be second order in Cu^{2+}, and, in the presence of Li^+ (which can form a SAT but not a MP), a term first order in Li^+ and Cu^{2+} was demonstrated.[7] The interpretation was that one metal forms a SAT species with the free base TPyP, and, after a central proton is lost from a pyrrole nitrogen in the SAT, a second metal ion inserts from the distal side to form the MP. We report data which indicate that all of the aqueous solution results that heretofore indicated the existence of SAT complexes with TPyP can be explained in a reasonable fashion without the notion of "sitting-atop" entities. Such evidence arose from a study of the insertion of copper ions into the monomeric and fully water soluble[8,9] tetrakis(N-methylpyridyl)porphine (TMTPyP).

Experimental Section

TMTPyP was synthesized by literature methods.[8,9] The kinetics were determined using a Beckman Acta III recording spectrophotometer with a thermostated cell compartment for slow reactions and a Durrum-Gibson stopped flow apparatus for faster reactions. The kinetics were followed under pseudo-first-order conditions with greater than a 40-fold excess of total metal ion to total porphyrin. The pseudo-first-order rate constant, k_o, was calculated as described previously.[6] In general the 550-nm CuP peak was monitored, and the same rate constant could also be obtained by following the decrease in the free base 520-nm band. The reagents were standard-
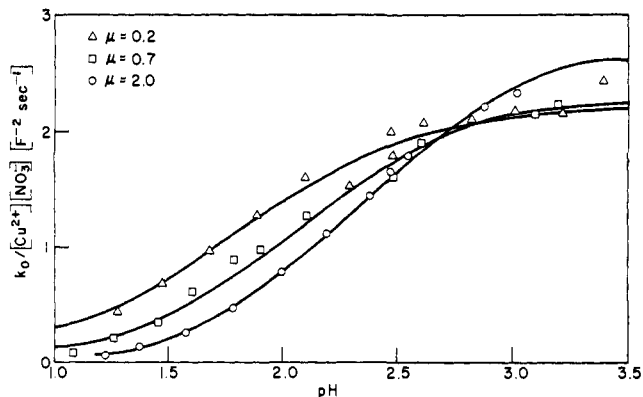
(4) B. F. Burnham and J. J. Zuckerman, J. Amer. Chem. Soc., 92, 1547 (1970).
(5) A. L. Stone and E. B. Fleischer, J. Amer. Chem. Soc., 90, 2735 (1968).
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(9) P. Hambright and E. B. Fleischer, Inorg. Chem., 9, 1757 (1970).

ized by conventional methods. Nitrate salts were used, as perchlorates precipitate TMTPyP. The CuP product was not converted into the diacid by 1.0 M HNO_3 in periods under 5 days at 25°.
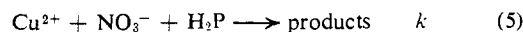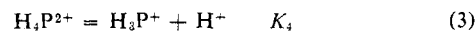
Results

At a constant copper ion concentration, pH, and ionic strength $(NaNO_3)$, the kinetics of the CuP formation were found to be first order in porphyrin, with the rate constant independent of total porphyrin over a fivefold range $(1.2-6.7 \times 10^{-5} M)$. At pH 3.1 with a constant copper concentration, the graph in Figure 1 shows that the observed rate is first order in "neutral salt," with KNO_3, $NaCl$, and $NaNO_3$ up to ca. 1.8 M. While the reaction between the dipositive Cu^{2+} and tetrapositive (owing to the four $N-CH_3^+$ groups) TMTPyP should increase with ionic strength, it also should be possible to extrapolate the observed rate to zero as the salt concentration goes to zero. This is interpreted as an anion term in the rate law, since the potassium and sodium nitrate rates are similar and very different from that of $NaCl$. There is also no evidence for species such as $(Cu(NO_3)^+)$ at low nitrate concentrations.[10]

At pH 2.1, $= \mu$ 2.0 $(NaNO_3)$, the observed rate was first order in total copper over a 1600-fold dilution $(0.5-3 \times 10^{-4} M)$. The kinetics were then run as a function of pH at ionic strengths of 0.2, 0.7, and 2.0 $(NaNO_3)$. The observed rate constant, k_o, was found to be of the form

$$k_o = \frac{k[Cu^{2+}][NO_3^-]}{(1 + [H^+]/K_3 + [H^+]^2/K_3K_4)} \quad (2)$$

Figure 2 is a graph of $(k_o/[Cu^{2+}][NO_3^-])$ vs. pH at different ionic strengths. The solid theoretical curves were calculated using the values of k, K_3, and K_4 listed in Table I. pK_3 and pK_4 are found to increase with ionic strength. The mechanism of the reaction is assumed to be

$$H_4P^{2+} = H_3P^+ + H^+ \quad K_4 \quad (3)$$

$$H_3P^+ = H_2P + H^+ \quad K_3 \quad (4)$$

$$Cu^{2+} + NO_3^- + H_2P \longrightarrow products \quad k \quad (5)$$

With step 5 as rate determining and steps 3 and 4 as

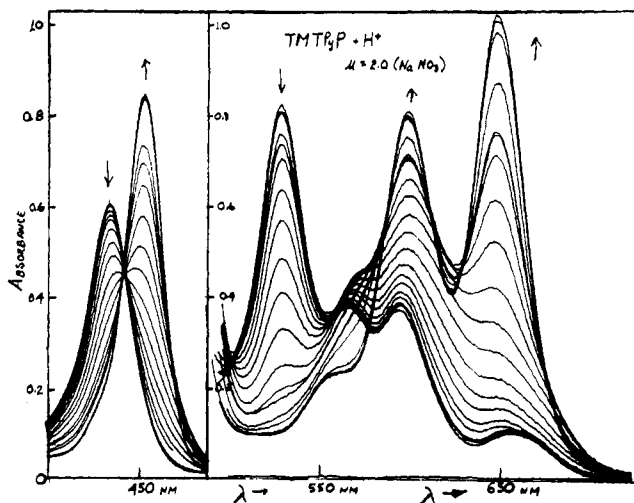(10) L. G. Sillen and A. E. Martell, Chem. Soc. Spec. Publ., No. 17 (1964); Suppl 1, No. 25 (1971).

Figure 3. Absorption spectra of TMTPyP when titrated with HNO₃ at μ = 2.0 (NaNO₃), 26°. The spectra are from pH 7.0 to 0.2, and the arrows indicate the band direction as the pH is decreased. The Soret was run in 1-cm cells and the visible in 10-cm cells, at the same concentration of TMTPyP (5.9 × 10⁻⁶ M).

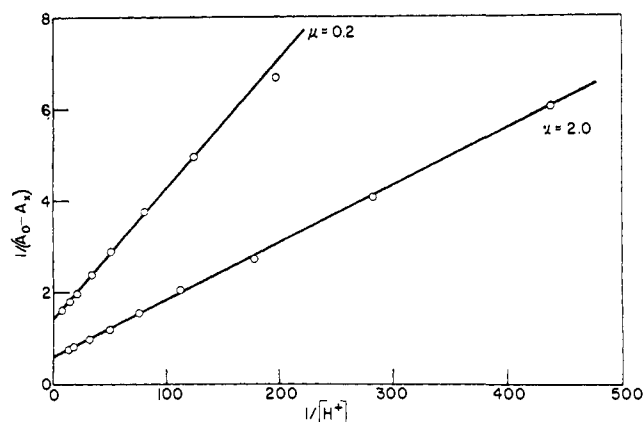Figure 4. Plot of $1/(A_0 - A_x)$ vs. $1/[H^+]$ to determmie K_3 from eq 6. The wavelength is 522 nm for both μ = 0.2 and 2.0.

Table I. Summary of Rate and Equilibrium Data as a Function of Ionic Strength for TMTPyP, 26°

Reaction	Ionic strength[a]	pK₃[b]	pK₄[b]	$k, F^{-2} \text{ sec}^{-1}$
Cu²⁺–TMTPyP	0.2	1.7	0.4	2.3 ± 0.3
	0.7	2.0	0.7	2.3 ± 0.3
	2.0	2.5	1.0	3.1 ± 0.4
Zn²⁺–TMTPyP[c]	0.7	2.1	0.8	(4.9 ± 0.1) × 10⁻²
H⁺–TMTPyP	0.2	1.4	<1	
	2.0	2.2	0.9	
	?[d]	1.5	0.7	

[a] Controlled with NaNO₃. [b] pK values ±0.1 pH unit. [c] Reference 11. [d] Values quoted in ref 8.

rapid preequilibria between the diacid, monocation, and free base forms of TMTPyP, eq 2 can be readily derived.

Spectrophotometric titrations from 400 to 700 nm of TMTPyP with HNO₃ were done at ionic strengths of 2.0 and 0.2 (NaNO₃). The data for the μ = 2.0 and 0.2 (NaNO₃) reactions are shown in Figure 3. The spectra do not show a consistent set of isosbestic points which are pH invariant, and thus more than
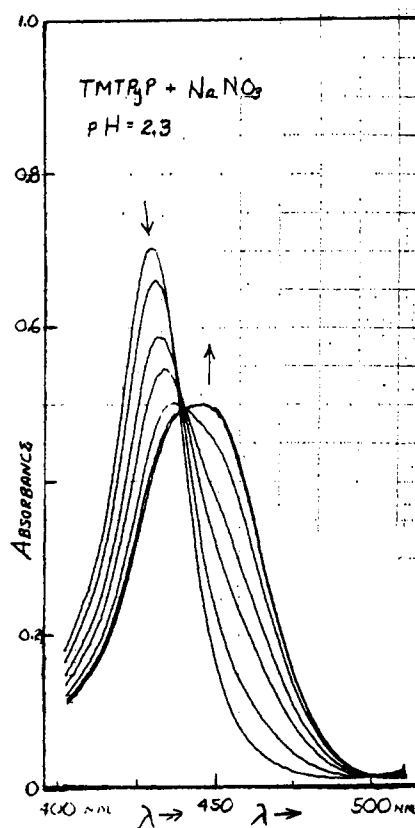

Figure 5. A spectrophotometric titration in the Soret region of TMTPyP (pH 2.3) with increasing amounts of NaNO₃. The concentrations are 10⁻²·³, 9.0 × 10⁻², 4.5 × 10⁻¹, 9.0 × 10⁻¹, 1.8, 2.7, and 4.7 M.

two protonated porphyrin species must be present between pH 0.5 and 7.

Using the absorbance changes at high pH at 522 nm, K_3 can be calculated from the equation

$$\frac{1}{(A_0 - A_x)} = \frac{K_3}{(A_0 - A_\infty)[H^+]} + \frac{1}{(A_0 - A_\infty)} \quad (6)$$

At a constant wavelength, A_0 and A_∞ are the absorbances of the free base and monocation forms of the porphyrin, and A_x that of a mixture of H₃P⁺ and H₂P. The linear relationship between $(1/(A_0 - A_x))$ and $(1/[H^+])$ is shown in Figure 4, and the results are given in Table I. K_4 was estimated from the low pH absorbances that occurred at 560 nm. The agreement between the kinetic (both Cu²⁺ and Zn²⁺)[11] and equilibrium determinations of pK_3 and pK_4 as a function of ionic strength (Table I) is satisfactory.

In a spectrophotometric titration of the free base TMTPyP at pH 7 with NaNO₃ (10⁻⁷–3.8 M), the entire Soret band simply shifted a total of ca. 5 nm to shorter wavelengths as NO₃⁻ increased, with no decrease in band intensity. At pH 2.3, typical titration spectra is shown in Figure 5. As NO₃⁻ increases, the 422-nm free base band decreases, with a new band forming at 422 nm. Exactly the same peak positions and lack of a single Soret isosbestic point are also found in the (H⁺) titration of TMTPyP shown in Figure 3. Qualitative work indicated that the Soret changes depend on the type of cation in terms of its ionic strength,

(11) H. Baker and P. Hambright, unpublished results.

with trivalent metal nitrates giving a larger Soret change than 1 : 1 electrolytes at the same concentration.

By use of eq 6 on the 422-nm peak in the NaNO₃ titration (Figure 5), an apparent formation constant of *ca.* 1 could be estimated for NaNO₃ concentrations from 9×10^{-2} to 2.7 *M*. Between 2.7 and 3.7 *M* NaNO₃ there was no further change in absorbance. The "formation constant" appears to be fortuitous, however, since $(A_0 - A_\infty)$ from eq 6 (0.414) was in total disagreement with that observed in Figure 5 (0.292). It should be noted that the same procedure was used to calculate "sitting-atop" equilibrium constants[6] with TPyP, which shows a formation constant for Na⁺ of *ca.* 2.3 M^{-1}.

Discussion

Both the present kinetic and equilibrium data indicate that TMTPyP can exist from pH 0 to 7 as the diacid, monocation, and free base forms, in contrast to previous interpretations[9] of only a diacid–free base equilibrium. The apparent acid range equilibrium constant reported[9] for TMTPyP was the same as that[12] of TPyP, and thus both porphyrins apparently behave in the same fashion. The earlier work was done by analyzing the Soret region bands, and, as shown in Figure 4, it is not difficult to mistake one isosbestic point for a region of closely overlapping curves. The visible region, however, certainly shows that more than two species are present, as was noted by Pasternack and coworkers.[8] The point of interest here is that the pK values increase with an increase in ionic strength.

The rate law for copper incorporation into TMTPyP indicates that the diacid and monocation forms are, as expected,[13,14] unreactive and that a nitrate anion is present in the rate law. Such anion catalysis has not been noted in formation reactions before,[2] and could arise here because of the four positive N-methyl groups on the porphyrin periphery. The anion may stabilize the activated complex by reducing the formally 6 + charge owing to the metal and porphyrin.[15] The rate law for the acid catalyzed solvolysis[16] of ZnTMTPyP is second order in (H⁺) and also first order in (NO₃⁻). Thus the composition of the activated complex for metal ion incorporation and dissociation with this porphyrin is the same.

If the anion concentration was not kept constant, or accounted for in the rate law, the Cu–TMTPyP reaction would appear to be second order in total copper. This is apparently what happened in the study of metal ion incorporation into TPyP, where the second-order metal ion dependence observed was a feature of the postulated "sitting-atop" behavior.[6] The unexplained inverse proton dependence in the TPyP reaction[6] (where only $H_1P^{2+}-H_2P$ should have been present) and other TPyP reactions[17] studied in HClO₄–

HAc is now reasonably understood as the lack of reactivity of the monocation, which exists in the high pH ranges studied.

The observation of the shift in the Soret band of TPyP at pH 2 upon titration with metal salts, which led to the calculation of metal ion porphyrin SAT formation constants,[6] is also readily explained. At pH 2 with low ionic strengths, the free base form TPyP would predominate. As the salt concentration is increased, pK_3 and pK_4 increase, with a corresponding decrease in the amount of free base relative to mono- and dication forms at constant pH, and a corresponding change in the absorption spectra occurs. As noted in the Results section, little change in spectra takes place upon salt addition at pH 7, where pK_3 and pK_4 are about 4 pH units below[7], even at high ionic strengths. The SAT behavior postulated previously[6] is thus partially owing to a strong secondary salt effect.

The rate law for metal ion addition to TPyP showed a second-order dependence on entering metal ion,[6] and another term first order in entering ion and first order in "inert" metal ion with high concentrations of inert salts.[7] In present terms, we are simply observing the first order depending on metal ion and anion that these porphyrin types require. The fact that the rate of the Cu–TPyP reaction becomes independent of LiNO₃ at high nitrate concentrations at constant pH is also readily rationalized. At a given pH below 3 (Figure 2), the higher ionic strength reactions are slower because less free base is present at a given pH. This effect does not continue indefinitely since, as shown in Figure 5, the amount of free base reaches a minimum above 2.7 *M* NaNO₃. Thus a plot of $k_o/[Cu^{2+}][NO_3^-]$ at constant pH becomes independent of NO₃⁻ around 3 *M* for TMTPyP, and the same can be shown with the published data[7] for Cu–TPyP in the presence of LiNO₃.

The observation of anion terms in the rate law demonstrated here with Cu–TMTPyP and previously with H⁺–ZnTMTPyP and the lack of such behavior with other porphyrin molecules[1] indicate that the formation and dissociation mechanisms of metal ions and porphyrins are probably not all the same. Such mechanisms apparently depend on the porphyrin type and may be because of the charge on the porphyrin periphery. Thus negatively charged porphyrins aggregate in aqueous solution[8] whereas some positively charged porphyrins apparently are completely monomeric. Similarly, in axial ligand substitution studies on iron porphyrins, negatively charged porphyrins favor the substitution of imidazolium ion over imidazole,[18] whereas the reverse is noted with iron porphyrins bearing positive peripheral substituents.[19] At present, too few systems have been investigated to make many general statements about reactivities.

In conclusion, "sitting-atop" complexes do not exist in aqueous solution with TPyP or TMTPyP. The sitting atop phenomenon is explained by (1) an unusual anion term in the incorporation rate law, (2) the strong increase in pK_3 and pK_4 upon increase in ionic strength, and (3) the lack of reactivity of the diacid and monocation forms toward metal ions. Thus the pathway

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(13) J. Weaver and P. Hambright, *Inorg. Chem.*, 8, 167 (1969).
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(15) The ions Co²⁺, Mn²⁺, and Ni²⁺ also show nitrate catalysis. With Zn(Py)²⁺ and Zn(Py)₂²⁺, all terms are nitrate catalyzed. With Zn(OAc)⁺ and Zn(OAc)₂, the rate law shows both anion dependent and independent terms. With Zn(NH₃)₄²⁺ and TMTPyP, apparently only the dianion (P²⁻) is reactive and no nitrate catalysis is observed. Thus over a wide range of species, no formal 6 + charged activated complex for TMTPyP has been found: P. Hambright, unpublished data.
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(17) E. I. Choi and E. B. Fleisher, *Inorg. Chem.*, 2, 94 (1963).
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(19) G. B. Kolski and R. A. Plane, *J. Amer. Chem. Soc.*, 94, 3740 (1972).

5946

of incorporation of metal ions into the "SAT" complexes of TPyP is through the free base form, which is always in equilibrium with the di- and mono-cations. Several groups have done temperature-jump kinetic studies on TPyP with various cations and found no relaxations in the range that could be ascribed to SAT equilibria of the sort postulated.[6] This is because the proton equilibria actually present are too fast to measure by such methods.[20]

(20) R. R. Das, R. F. Pasternack, and R. A. Plane, *J. Amer. Chem. Soc.*, 92, 3312 (1970).

SAT complexes, adducts between metal ions and porphyrins which form prior to metal ion incorporation, have not been demonstrated either in aqueous or nonaqueous[9] solution. The sitting-atop notion must now be regarded as indicating a probable but yet unobserved configuration of the system along the reaction coordinate toward metalloporphyrin formation.

An Estimate of the Barriers Hindering Rotation about the Cα–C' Bond between the Cis' and Trans' Conformations in an Isolated L-Proline Residue

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Abstract: The barriers to rotation about the C^α–C' bond between the cis' ($\psi \approx 125°$) and trans' ($\psi \approx 325°$) minimum energy conformations in an isolated trans peptide bond L-proline residue are estimated using semiempirical potential functions. Nonbonded repulsive and London dispersion interactions are evaluated using a 6–12 potential, while electrostatic interactions are treated in the monopole–monopole approximation. Contributions made by hydrogen bonding between the carbonyl oxygen preceding and the amide proton succeeding the pyrrolidine ring are accounted for by the method of Brant. In addition, valence angle distortion and peptide bond rotation resulting in nonplanar conformations are considered. All bond lengths are fixed, while the valence angles and the angles of rotation φ, ψ, and ω are varied. The calculated barriers at ψ = 60 and 210° between the cis' and trans' conformations are found to be significantly lower than the cis–trans barrier (*ca.* 20 kcal/mol) about the peptide bond. In fact, both barriers are less than 10 kcal/mol and would not lead to separate nuclear magnetic resonances (one for cis' and another for trans') at room temperature. Distortion of the valence angles from their crystalline values, which greatly relieve the steric interactions of the proline carbonyl group and the N–H group succeeding the pyrrolidine ring with the β-CH₂ group of the pyrrolidine ring and with the carbonyl group preceding the pyrrolidine ring, and when $\psi \approx 210°$, the intramolecular hydrogen bond between the carbonyl group preceding and the N–H group succeeding the pyrrolidine ring, as suggested previously, account for the small barriers.

During the course[1-12] of determining the solution conformations of several cyclic peptides (synthetic[1-6] and biologically active[7-11]) containing isolated L-proline residues (an L-proline residue not succeeded by another proline residue[13]) using nuclear magnetic resonance spectroscopy (nmr) and conformational energy estimates, the question of the magnitude of the barrier to rotation about the C^α–C' bond (see

Figure 1) between the cis' (ψ = 125°) and trans' (ψ = 325°) minimum energy conformations[14] became important (see ref 12 for a review of cyclic peptide conformation). If the barriers are of a magnitude similar to the cis–trans peptide bond barrier,[17] *ca.* 20 kcal/mol, then separate nuclear magnetic resonances could be expected for the cis' and trans' conformations of the L-prolyl residues, because both conformations have nearly the same energy.[13,18] On the other hand, if both barriers (at $\psi \approx$ 60 and 210°) are much larger

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