

Copper Incorporation into Picket Fence Porphyrin Isomers

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The picket fence porphyrin, meso-tetra($\alpha,\alpha,\alpha,\alpha$ -*ortho*-pivalamidophenyl)porphyrin [1] and its derivatives [2] have played important roles as models in hemoglobin and myoglobin oxygenation processes. Such porphyrins, with bulky groups on one side of the porphyrin ring, are in contrast to normal porphyrins, where both faces are exposed. With the aim of further delineating the features of porphyrin metalation reactions, we report a study of copper incorporation into the four rotational isomers of the free base picket fence porphyrins.

Experimental

The four rotational isomers of T(*o*-NH₂)PP were separated on preparative silica gel TLC plates, and reacted with trimethylacetyl chloride to form the four picket fence porphyrins, after the method of Collman and co-workers [1]. The kinetics of copper perchlorate incorporation [3] into the isomers in

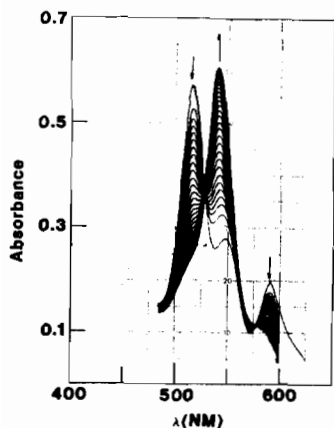


Fig. 1. Isobestic points found during the course of the reaction of Cu²⁺ and the picket fence T($\alpha,\alpha,\alpha,\alpha$ -*o*-((CH₃)₃-CONH))PP in DMF, 25 °C.

TABLE I. Rate Data for Copper Incorporation, 25 °C, DMF.

Porphyrin	k (M ⁻¹ sec ⁻¹)
T($\alpha,\alpha,\alpha,\alpha$ - <i>o</i> -((CH ₃) ₃ CONH))PP	4.6 × 10 ⁻⁴
T($\alpha,\alpha,\alpha,\beta$ - <i>o</i> -((CH ₃) ₃ CONH))PP	3.8 × 10 ⁻⁴
T($\alpha,\alpha,\beta,\beta$ - <i>o</i> -((CH ₃) ₃ CONH))PP	3.0 × 10 ⁻⁴
T($\alpha,\beta,\alpha,\beta$ - <i>o</i> -((CH ₃) ₃ CONH))PP	3.4 × 10 ⁻⁴
T(<i>o</i> -NH ₂)PP	7.0 × 10 ⁻²
T(<i>p</i> -((CH ₃) ₃ CONH))PP	6.0 × 10 ⁻²
T(<i>p</i> -CH ₃ CONH))PP	5.0 × 10 ⁻²
T(<i>p</i> -H)PP	2.6 × 10 ⁻²
T(<i>p</i> -CN)PP	1.0 × 10 ⁻²

DMF at 25 °C were studied spectrophotometrically by standard techniques.

Results and Discussion

Figure 1 shows the excellent isobestic points found in the visible region during the Cu²⁺/ $\alpha,\alpha,\alpha,\alpha$ -isomer reaction. Similar results were found for each isomer, indicating that only the free-base H₂-P and Cu-P forms were in appreciable concentration. The rate law for the picket fence isomers and other porphyrins studied was first order in metal and free base porphyrin.

Table I shows the rate data found for copper incorporation into the porphyrins. The *ortho*-substituted picket fence porphyrins are observed to be at least one-hundred times less reactive with copper than their *para*-substituted counterpart. Assuming that copper with its coordination shell cannot approach the picket side of the $\alpha,\alpha,\alpha,\alpha$ and $\alpha,\alpha,\alpha,\beta$ isomers, the relative *para/ortho* ratio is still substantial.

A variety of factors can be advanced to rationalize such rate differences. For *para* substituted porphyrins, metal incorporation rates increase somewhat with an increase in porphyrin basicity [4–6]. This basicity can in many cases be related to E_{1/2}⁺(1), the first reduction potential of the free base porphyrin to its mono-anion form [7, 8]. Directly determined pK [9] values (H₄-P²⁺/H₂-P) show the T(*o*-CH₃)PP to be less basic (pK = 0.78) than the T(*p*-CH₃)PP (pK = 1.85), and T(*o*-CH₃)PP reacts about five times less rapidly with zinc [10] and copper ions [5] than does T(*p*-CH₃)PP. For the copper reactions, T(*o*-CH₃)PP has a higher enthalpy and more positive entropy of activation than does T(*p*-CH₃)PP [5]. However since many porphyrin metallation [11] and exchange reactions [10] show

linear ΔH^\ddagger vs. ΔS^\ddagger plots, with isokinetic temperatures in the ambient range, small relative rate differences are not readily interpreted. From thermodynamic studies of zinc side-arm porphyrin ligations [12], it has been suggested that *ortho* substituted porphyrins may be less solvated on the substituent porphyrin face than is the case with *para* substituted derivatives.

On the basis of reduction potentials [7], although the $\alpha,\alpha,\alpha,\alpha$ picket fence porphyrin is less basic than would be predicted only considering sigma substituent constants, this factor alone presumably cannot account for all of the rate differences found.

To explain such results, it is noted that predeformed central N-methyl etioporphyrin-III [13] and N-methyltetraphenylporphyrin [3] react with metal ions 10^3 to 10^5 times faster than do their unmethylated counterparts. This has been interpreted in part as the requirement for porphyrins to deform before metal ion incorporation. Such deformation might both place the porphyrin nitrogen atoms in bonding positions, and uncouple the N-H tautomerism in the free base porphyrins. Such tautomerism rates appear to be independent of porphyrin basicity with substituted tetraaryl porphyrins [14]. Porphyrin deformation has also been suggested as important in proton addition to free base porphyrins [15]. In these terms, picket fence porphyrins, with their large pickets perpendicular to the porphyrin plane and hydrogen bonded to the solvent, may be less deformable, and hence less reactive than normal porphyrins.

Another factor is proton dissociation of the central nitrogen atoms. The form of the metallation rate laws in water indicates that the porphyrin free base protons are not lost before the rate-determining step, and suggestions have been made that proton loss and ligand desolvation from the metal occur in the rate limiting step [6]. Insofar as the $\alpha,\alpha,\alpha,\alpha$ -isomer may not allow a ready exchange of solvent molecules on the picket side of the porphyrin to stabilize dissociated protons, the metal incorporation rates might be expected to be slower. The lack of accessibility to the reaction site by both bases and metal ions due to the pickets themselves might explain why the

$\alpha,\alpha,\alpha,\alpha$ - and $\alpha,\alpha,\alpha,\beta$ - isomers react faster than the $\alpha,\alpha,\beta,\beta$ - and $\alpha,\beta,\alpha,\beta$ - forms.

DMF is less than ideal for metallation studies, and was simply chosen due to the mutual solubility of the metal and these porphyrins. Preliminary results, however, indicate that water soluble picket fence porphyrins show the same reactivity features [16].

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