

## A Rapid Porphyrin Metallation

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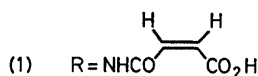
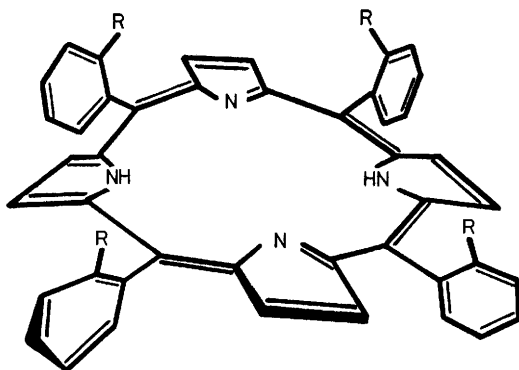
**Summary** In aqueous dimethylformamide solution *meso-αααα*-tetra(*o*-maleamoylphenyl)porphyrin undergoes rapid metal incorporation (Cu<sup>II</sup>, Zn<sup>II</sup>, Co<sup>II</sup>, and Ni<sup>II</sup>) by a mechanism featuring rate-determining intramolecular transfer of the metal ion from the carboxylate binding site to the porphyrin nucleus.

THE abnormally slow rates of metal ion incorporation into porphyrins are generally discussed in terms of a weak outer-sphere association between the reactants followed by rate-determining desolvation of the metal and/or deformation of the rigid planar porphyrin framework.<sup>1</sup> This

suggests that greatly increased rates of metallation might be found for systems which provide an appended binding site such that the metal is held in close proximity to the porphyrin nucleus. We report that this expectation is indeed realized in the reactions of the tetra-carboxylic acid 'picket fence' porphyrin (**1**).

Treatment of *meso-αααα*-tetra(*o*-anilino)porphyrin<sup>2</sup> in dimethylformamide (dmf) with excess of maleic anhydride under dinitrogen and in the absence of light gave on work-up and crystallization (CHCl<sub>3</sub>-heptane) *meso-αααα*-tetra(*o*-maleamoylphenyl)porphyrin† (**1**) ([porphH<sub>2</sub>-O<sub>4</sub>H<sub>4</sub>]) in 90% yield; homogeneous by t.l.c. (CHCl<sub>3</sub>-MeOH-HOAc, 7:2:1); λ<sub>max</sub> (dmf) 646, 591, 551, 518, and 419 nm (Soret).

† Satisfactory C, H, and N analyses, and <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra were obtained. Details will be reported elsewhere (D. A. Buckingham, C. R. Clark, and W. S. Webley).



In dmf-water (50% w/w) buffered above pH 4 the porphyrin ( $10^{-4}$ – $10^{-5}$  mol dm $^{-3}$ ), initially present as the monomeric tetra-anion [porphH $_2$ O $_4$ ] $^{4-}$ , reacts rapidly ( $t_{\frac{1}{2}} < 0.2$  s) with copper(II) perchlorate ( $10^{-2}$  mol dm $^{-3}$ ) to produce the corresponding copper(II) porphyrin ( $\lambda_{\text{max}}$  544 nm, single spot on t.l.c.). Kinetic studies in the pH range 4.2–6.5 (544 nm,  $5 \times 10^{-3}$  to  $2 \times 10^{-2}$  mol dm $^{-3}$  Mes or Hepes buffer, 25 °C,  $I$  0.1 mol dm $^{-3}$ , Et $_4$ NClO $_4$ ) revealed the following general features for Cu(II) insertion. (i) At constant pH and increasing copper(II) concentration the observed first-order rate constant increases to reach ultimately a [Cu $^{2+}$ ]-independent plateau (Figure, a). (ii) Under conditions of metal ion-saturation a plot of  $k_{\text{obs}}$  vs. pH exhibits a pH-independent region (pH 4.2–5.5) with a rate dependence inverse in hydrogen ion activity at higher alkalinity (Figure, b). These observations lead to the rate law for metal incorporation in equation (1), and are

$$k_{\text{obs}} = \frac{\{K_1[\text{Cu}^{2+}]/(1 + K_1[\text{Cu}^{2+}])\}}{(k_1 + k_2K_a/a_{\text{H}^+})} \quad (1)$$

consistent with the mechanism in the Scheme.†

Rapid complexation of copper(II) by the carboxylate site [ $K_1 = (1.5 \pm 0.2) \times 10^3$  dm $^3$  mol $^{-1}$ ] is followed by rate-determining metal-ion transfer from the O $_4$  site to the porphyrin nucleus either by path 1 as Cu $^{2+}$  ( $k_1 = 5.6$  s $^{-1}$ ), or by path 2 as CuOH $^+$ § ( $k_2 = 1.1 \times 10^5$  s $^{-1}$ ,  $K_a = 10^{-10}$  mol dm $^{-3}$ , estimated). Thus intramolecular transfer of CuOH $^+$  is favoured over transfer of Cu $^{2+}$  by a factor of ca.  $2 \times 10^4$ . A possible role for co-ordinated hydroxide in the former process is to act as an intramolecular general base to facilitate metal entry through deprotonation of pyrrole NH.

† The final reaction product is in fact [Cu(porph)-Cu(O $_4$ )] $^{2-}$  since the O $_4$  site left vacant on metal transfer subsequently binds additional Cu $^{2+}$  in a fast equilibrium step. The [Cu(porph)-(O $_4$ )] $^{4-}$  and [Cu(porph)-Cu(O $_4$ )] $^{2-}$  complexes exhibit very similar visible spectral characteristics.

§ This mechanism is preferred to one involving its kinetic equivalent of specific hydroxide ion catalysis. Pathways comparable to the latter have not been observed previously, even for metallations using strongly basic aqueous media; ref. 3.  $K_a$  for the OH $_2$ -CuO $_4^{2-}$  system is expected to be somewhat smaller than the value of  $2.5 \times 10^{-10}$  mol dm $^{-3}$  found for the OH $_2$ -CuO $_3$ N $^{1-}$  moiety in coppernitrioltriacetate mono-anion (D. Hopgood and R. J. Angelici, *J. Am. Chem. Soc.*, 1968, **90**, 2508).

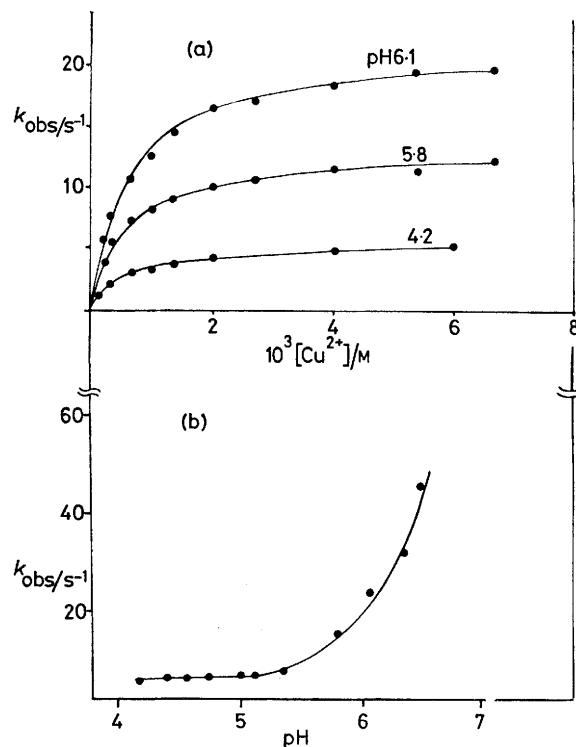
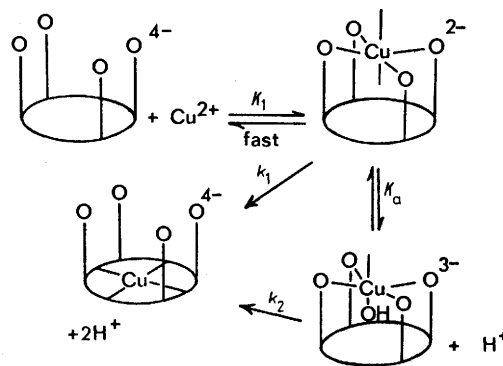


FIGURE. Variation of the first-order rate constant for Cu $^{2+}$  insertion into [porphH $_2$ O $_4$ ] $^{4-}$  in 50% w/w dmf-water at 25 °C: (a) as a function of copper(II) concentration at constant pH; (b) as a function of pH under metal ion-saturation conditions. Points are experimental and lines calculated using equation (1) and the values of the constants given in the text.

Saturation kinetics are also observed in the reactions of (1) with zinc(II), cobalt(II), and nickel(II), and the pH-independent rates of metal transfer ( $k_1 = 1.8$ , 0.1, and  $3 \times 10^{-4}$  s $^{-1}$  respectively) suggest that entry of M $^{2+}$  is



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controlled, at least in part, by the rate of ligand exchange on the metal.<sup>¶</sup> Apparently, at least for the  $k_1$  path, deprotonation of the pyrrole nitrogens occurs subsequent to the rate-determining step. This suggests a 'sitting atop' type intermediate for this pathway where the metal is bound to one or two pyrrole nitrogens, while a degree of binding to the  $O_4$  site is maintained.

Although many times slower than conventional ligand substitution processes<sup>4</sup> these reactions are the fastest yet observed for a tetraphenylporphyrin system, and represent

the first example of an intramolecular mechanism for metal ion incorporation. The results may have some relevance to the mode of action of the enzyme ferrochelatase which catalyses the insertion of  $Fe^{II}$ ,  $Cu^{II}$ ,  $Zn^{II}$ ,  $Ni^{II}$ ,  $Co^{II}$ , and  $Mn^{II}$  into protoporphyrin IX.<sup>5</sup> Our results suggest that the associated protein environment provides metal binding sites sufficiently close to the porphyrin nucleus to allow rapid metallation under the mild physiological conditions.

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<sup>¶</sup> Rates of exchange for water or carboxylate ligands follow the sequence  $Cu^{2+} > Zn^{2+} > Co^{2+} > Ni^{2+}$ ; ref. 4.

<sup>1</sup> W. Schneider, *Struct. Bonding (Berlin)*, 1975, **23**, 123; P. Hambright in 'Porphyrins and Metalloporphyrins,' ed. K. M. Smith, Elsevier, Amsterdam, 1976, ch. 6; F. Longo in 'The Porphyrins,' Vol. 5, ed. D. Dolphin, Academic Press, New York, 1978, ch. 10.

<sup>2</sup> J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang, and W. T. Robinson, *J. Am. Chem. Soc.*, 1975, **97**, 1427.

<sup>3</sup> J. Turay and P. Hambright, *J. Inorg. Nucl. Chem.*, 1979, **41**, 1385.

<sup>4</sup> M. Eigen and R. G. Wilkins, *Adv. Chem. Series*, 1965, **49**, 55.

<sup>5</sup> M. S. Jones and O. T. G. Jones, *Biochem. J.*, 1970, **119**, 453.