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meso-Tetra[5-(8-hydroxyquinolyl)]porphine. A Novel Porphyrin with Metal-chelating Groups in the Peripheral Region

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meso-Tetra[5-(8-hydroxyquinolyl)]porphine was synthesized by the Rothemund method as a model of porphyrin with metal chelating groups in the peripheral region. The presence of three kinds of copper(II) complexes was demonstrated; free base porphyrin with metal chelated 8-quinolinol groups and metalloporphyrin with metal chelated and unchelated 8-quinolinol groups. In dimethylformamide solution, reaction of the compound with excess copper(II) perchlorate occurred in two steps; rapid metal chelation of the 8-quinolinol moiety and subsequent slow Cu(II) incorporation into the porphine moiety. Reaction with excess aluminum(III) nitrate under similar conditions gave free base porphyrin with Al(III) chelated 8-quinolinol groups.

Keywords——porphyrin; metalloporphyrin; tetraarylporphine; synthetic porphyrin; 8-quinolinol; metal chelation

It has been found that many human and animal tumors show porphyrin fluorescence and many naturally occurring porphyrins possess an affinity for neoplastic tissue.[2] Synthetic porphyrins such as tetraphenylporphinesulfonate have also been found to accumulate in tumors.[3] However, attempts to use porphyrin molecules as a carrier for radioactive metals in order to concentrate them in tumor tissue were unsuccessful.[4] Metalloporphyrins seem to lose the affinity for tumors.[5]

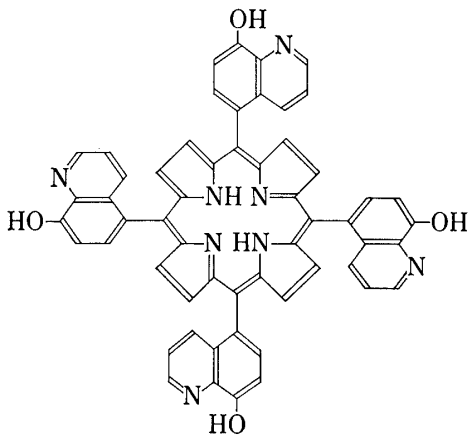

Fig. 1. Structure of *meso*-Tetra[5-(8-hydroxyquinolyl)]porphine

If the free base form of a porphyrin labeled with radioactive metals accumulates specifically in tumors, the potential uses of such a porphyrin in a diagnostic or chemotherapeutic role would be great; tumors could be imaged with external position or gamma cameras, destroyed by radiation from administered isotopes and sensitized such that they could be destroyed by an external stimulus. A porphyrin with a metal chelating group in the peripheral region might serve as such a carrier for radioactive metals.

As a model of porphyrins with metal chelating groups, *meso*-tetra[5-(8-hydroxyquinolyl)]porphine (Fig. 1) has been synthesized. This article deals with its

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2) M. Tsutsui, C.J. Carrano, and E.A. Tsutsui, *Ann. N.Y. Acad. Sci.*, **244**, 774 (1975).

3) J. Winkelman, *Cancer Res.*, **22**, 589 (1962); J. Winkelman, G. Slater, and J. Grossman, *ibid.*, **27**, 2060 (1967).

4) J. Winkelman, J.G. McAfee, H.N. Wagner Jr., and G.R. Long, *J. Nucl. Med.*, **3**, 249 (1962); J. Winkelman, S. Rubenfeld, and J.G. McAfee, *ibid.*, **5**, 462 (1964).

5) P. Hambright, P. Fawwaz, P. Valk, J. McRae, and A.J. Bearden, *Bioinorganic Chem.*, **5**, 87 (1975).

synthesis and with the characteristics of the chelation phenomena. Biological and medical applications of the compound will be reported later.

Results and Discussion

The Rothemund method,[6] *i.e.*, the direct condensation of pyrrole and a corresponding aldehyde, was employed for the synthesis of *meso*-tetra[5-(8-hydroxyquinolyl)]porphine. The compound may be represented as $PH_2(QOH)_4$. PH_2 stands for the porphine moiety with two pyrrole hydrogens, and QOH for the quinolinol moiety.

Three kinds of metal complexes may exist for the compound; free base porphyrin with chelated 8-quinolinol groups, $PH_2(QOM)_4$, and metalloporphyrin with unchelated and chelated 8-quinolinol groups, $PM(QOH)_4$ and $PM(QOM)_4$, respectively, where M indicates a metal ion.

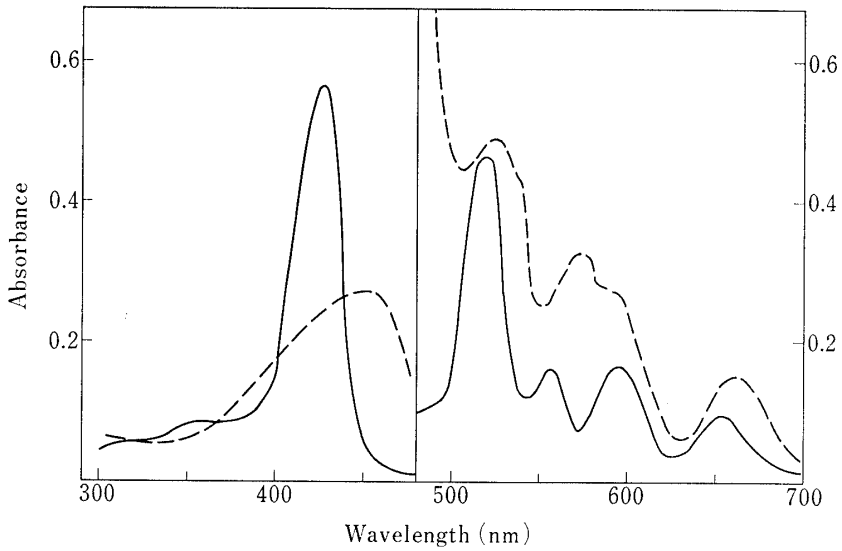

Fig. 2. Spectra of DMF Solutions of *meso*-Tetra[5-(8-hydroxyquinolyl)]-porphine (**1**)

Concentration of the porphine: 2×10^{-6} M, 300—480 nm; 2×10^{-5} M, 480—700 nm. A, metal ion-free solution. B, $[Cu(II)]_T$: 8×10^{-6} M, 300—480 nm; 8×10^{-5} M, 480—700 nm. A, ———; B, – – – –.

The spectrum of the compound in N,N-dimethylformamide (DMF) is shown as Curve A of Fig. 2. The compound is present as the free base form, $PH_2(QOH)_4$, in this solvent. Band III at 555 nm is less intense than band II at 594 nm[7] and the spectrum may be classified as phyllo-type, which is shown by unsubstituted porphine[8] and by *meso*-tetra(2- and 4-pyridyl)porphines.[9] It is clear from the spectrum that the porphine and the 8-quinilonol groups at the *meso* position are not conjugated and hence both rings are almost perpendicular, as in tetraphenyl and tetrapyridyl porphines. The low intensity of band III indicates the electron-withdrawing character of the 8-quinolinol groups.[9]

Spectrum B in Fig. 2 is that of DMF solution containing the porphine and four equivalents of Cu(II) perchlorate. The spectrum, with four weak bands in the visible region, is char-

6) P. Rothemund, *J. Am. Chem. Soc.*, **61**, 2912 (1939).
7) The visible bands of porphyrins are usually numbered I, II, III, and IV, starting from the low energy end.
8) A.I. Scott, "Interpretation of the ultraviolet spectra of natural products," Pergamon Press, Oxford, 1964, pp. 303—309; E.S. Stern and C.J. Timmons, "Electronic absorption spectroscopy in organic chemistry," 3rd Ed., Edward Arnold, London, 1970, pp. 174—179; K.M. Smith ed., "Porphyrins and metalloporphyrins," Elsevier, Amsterdam, 1975, pp. 19—28.
9) S. Sugata, S. Yamanouchi, and Y. Matsushima, *Chem. Pharm. Bull.*, **25**, 884 (1977).

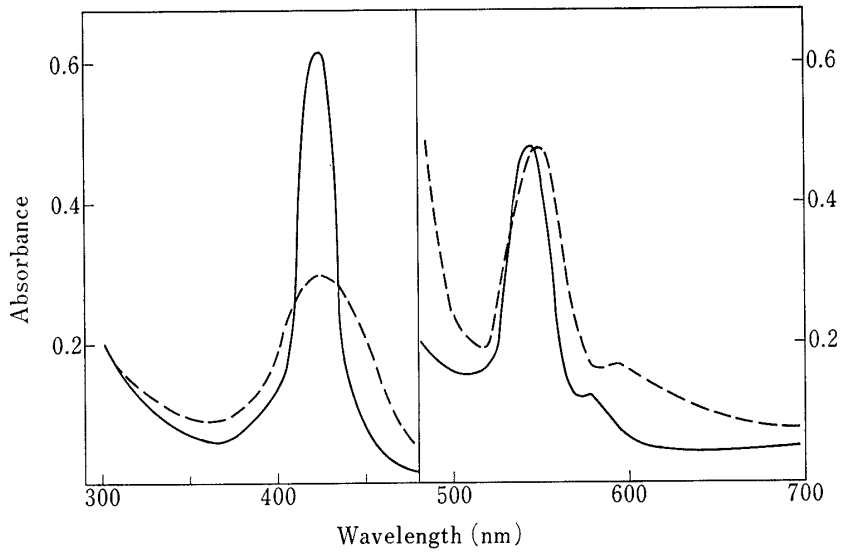

Fig. 3. Spectra of DMF Solutions of *meso*-Tetra[5-(8-hydroxyquinolyl)]-porphine (2)

C, D: Concentration of the porphine: 2×10^{-6} M, 300—480 nm; 2×10^{-5} M, 480—700 nm. $[Cu(II)]_T$: 1×10^{-4} M, 300—480 nm: 1×10^{-3} M, 480—700 nm. D: $[HClO_4]_T$, 6.2×10^{-2} M. C, – – – –; D, ———.

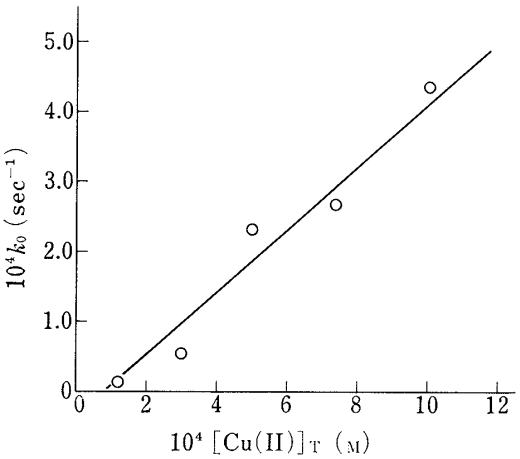

Fig. 4. Dependence of the Pseudo-First-Order Rate Constant, k_0, on the Total Concentration of Cu(II) Perchlorate, $[Cu(II)]_T$. $[PH_2(QOH)_4]_T$, 2×10^{-5} M

acteristic of the free base form of porphyrin. The difference spectrum between this spectrum (B) and that of $PH_2(QOH)_4$ (A) had a peak at 395 nm and resembled the difference spectrum between Cu(II) chelate and unchelated forms of 8-quinolinol. These results indicate that the predominant species in the DMF solution is $PH_2(QOCu^+)_4$. The spectrum of $PH_2(QOH)_4$ was regenerated by the addition of $HClO_4$ to the DMF solution ($[ClO_4)^-]=0.01$ M).

Cu(II) perchlorate (50 eq.) was added to the porphine in DMF. The spectrum measured immediately after the addition was essentially the same as that of $PH_2(QOCu^+)_4$. After standing 24 hr at 30°, the spectrum C in Fig. 3 was obtained. Spectrum C is quite similar to the characteristic spectrum of metalloporphyrin.[8] The species responsible for the absorption should be $PCu(QOCu^+)_4$.

The kinetics of formation of $PCu(QOCu^+)_4$ in DMF were measured at 30° by monitoring the absorption at 548 nm. With a large excess of total Cu(II) over porphine, the formation of the metalloporphyrin followed first-order kinetics. The observed first-order rate constant, k_0, increased linearly with increase of the total concentration of Cu(II)($[Cu(II)]_T$). Figure. 4 shows the intercept of the linear k_0 *vs* $[Cu(II)]_T$ plot at the axis. At $[Cu(II)]_T$ in four-fold excess over porphine, k_0 eventually approaches zero. It is concluded that the reaction of the porphine with excess Cu(II) consists of two steps; rapid metal chelation by the 8-quinolinol moiety and subsequent slow Cu(II) incorporation into the porphine moiety.

DMF solution of $HClO_4$ was added to the solution of $PCu(QOCu^+)_4$ to give 0.062 M total concentration of $HClO_4$. The spectrum characterisitic of metalloporphyrins, with intensified

Soret band, was obtained with this solution, as shown in Curve D of Fig. 3. The difference spectrum of D and C was quite similar to that of B and A and hence to that of Cu(II) chelate and unchelated forms of 8-quinolinol. Judging from these results, spectrum D can be ascribed to the species $PCu(QOH)_4$.

Fifty equivalents of $Al(NQ_3)_3$ was allowed to react with the porphine in DMF for 4 hr at 42°. The spectrum showed the presence of the free base form, $PH_2(QOAl^{2+})_4$. There was no sign of formation of Al porphinate, even on prolonged heating of the solution.

Cu(II) is the most reactive metal ion in porphyrin metallation under conditions similar to those used in the present study.[10] With other metal ions, metalloporphyrin formation is much slower and requires a large excess of metallic salts. On the other hand, chelation with 8-quinolinol is generally instaneous and complete. Thus, it seems feasible that the free base form of the porphine is labeled by a number of metallic elements.

Experimental

5-Formyl-8-quinolinol was prepared according to the method reported by Matsumura and Ito.[11] A propionic acid solution of 5-formyl-8-quinolinol (5.75 g, 0.0332 mol) and pyrrole (2.23 g, 0.0332 mol) was refluxed for 1.5 hr. After removal of the solvent *in vacuo*, the residue was washed and extracted with $CHCl_3$. The extract was chromatographed on a silica gel column and 300 mg of a purple crystalline product was obtained from the 2% MeOH–$CHCl_3$ eluate. The product was dissolved in 100 ml of EtOH–free $CHCl_3$ and refluxed for 2 hr. After addition of a dry benzene solution (2 ml) of 2,3-dichloro-5,6-dicyanobenzoquinone (60 mg), the mixture was refluxed for a further 2 hr. Purification by silica gel chromatography afforded 140 mg of *meso*-tetra[5-(8-hydroxyquinolyl)]porphine as purple crystals (yield 2%). *Anal.* Calcd for $C_{56}H_{34}N_8O_4$: C, 76.18; H, 3.88; N, 12.69. Found: C, 74.62; H, 4.00; N, 11.93. MS *m/e*: 882 (M^+), 738 ($M^+ - C_9H_6NO$). IR ν_{max}^{KBr} cm^{-1}: 3381 (QOH st.), 3311 (NH st.), 1580, 1502, 1470 (PH_2 C–N st.), 1418, 1265, 1239, 1192, 940 (PH_2, ring def.), 826, 788.

The compound was very soluble in DMF, dimethylsulfoxide, and 1 M HCl, soluble in $CHCl_3$, benzene, acetone, ethyl acetate, and dioxane, slightly soluble in MeOH, EtOH, AcOH, and 1 M NaOH, and insoluble in ether, CCl_4, and water.

The procedures used in the kinetic study were essentially the same as those described in our previous papers.[10]

A Union-Giken SM-202 spectrophotometer, a JASCO DS-701G infrared grating spectrophotometer, and a JEOL-01SG mass spectrometer were used throughout the present study.

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11) K. Matsumura and M. Ito, *J. Am. Chem. Soc.*, **77**, 6671 (1955).