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Porphyrins with Metal-Chelating Groups in the Peripheral Region. II.¹⁾ *meso*-Tetra[2-(8-hydroxyquinolyl)]porphine

SETSURO SUGATA and YOSHIKAZU MATSUSHIMA*

Kyoritsu College of Pharmacy, Shibakoen 1-5-30, Minato-ku, Tokyo 105, Japan

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meso-Tetra[2-(8-hydroxyquinolyl)]porphine was synthesized by the Rothmund method as a model of porphyrin with metal chelating groups in the peripheral region. The compound was soluble in dimethylformamide (DMF) but practically insoluble in water. Addition of Cu(II) perchlorate to the DMF solution resulted in biphasic spectral changes, an instantaneous change and a subsequent slow change. The spectrum after the first step showed the formation of the free base porphyrin with metal-chelated 8-quinolinol moieties. The second step was observable in the presence of a large excess of Cu(II) and was ascribed to the formation of the Cu(II)-porphyrin with Cu(II)-chelated 8-quinolinol. Addition of perchloric acid to the solution of the metalloporphyrin gave rise to the spectrum assignable to the Cu(II)-porphyrin with unchelated 8-quinolinol.

Keywords—porphyrin; Cu(II)-porphyrin; synthetic porphyrin; tetraarylporphine; 8-quinolinol; metal chelation

It is well known that many natural and synthetic porphyrins accumulate *in vivo* in neoplastic tissues,²⁾ though the affinity for the tissue seems to be lost in metalloporphyrins.³⁾ Porphyrins with metal-chelating groups in the peripheral region can be obtained as the free base form of the porphyrin labeled with radioactive or nonradioactive metal ions at the periphery. The potential uses of such porphyrins in medical sciences and analytical chemistry are many.

In the previous paper,¹⁾ we reported the synthesis of *meso*-tetra[5-(8-hydroxyquinolyl)]porphine as a model of such porphyrins. We have now prepared one of its isomers, *meso*-tetra[2-(8-hydroxyquinolyl)]porphine. The present paper describes the synthesis of

Fig. 1. Structures of *meso*-Tetra(8-hydroxyquinolyl)porphines

the new isomer, the chemical properties and chelation characteristics of the two isomers.

Results and Discussion

The Rothemund method,⁴⁾ which is a standard method for the preparation of *meso*-substituted porphyrins, consists of the direct condensation of pyrrole and a corresponding aldehyde in an appropriate solvent. *meso*-Tetra[2-(8-hydroxyquinolyl)]porphine ($\text{PH}_2\text{2}(\text{QOH})_4$) was prepared by the method in propionic acid. The yield (0.6%) was less than that (2%) of its 5-isomer, *meso*-tetra[5-(8-hydroxyquinolyl)]porphine ($\text{PH}_2\text{5}(\text{QOH})_4$).¹⁾

In this paper, the two porphyrins are represented by the symbols shown in the parentheses. PH_2 stands for the porphine moiety with two pyrrole hydrogens, and QOH for the quinolinol moiety. Three kinds of metal complexes are possible for these porphyrins. These are free base porphyrin with metal-chelated 8-quinolinol group ($\text{PH}_2(\text{QOM})_4$), metalloporphyrin with unchelated 8-quinolinol group ($\text{PM}(\text{QOH})_4$) and metalloporphyrin with metal-chelated 8-quinolinol group ($\text{PM}(\text{QOM})_4$), where M indicates a metal ion.

The visible absorption spectrum of $\text{PH}_2\text{2}(\text{QOH})_4$ in dimethylformamide (DMF) is shown in Fig. 2. The spectrum is quite similar to the characteristic spectrum of free base porphyrins, with an intense band at the 400-nm region (Soret band) and four weak bands at the longer wavelength side.⁵⁾ The four weak bands are usually numbered I, II, III and IV starting from the low-energy end. The ratio of the intensity of band III to that of band II in $\text{PH}_2\text{2}(\text{QOH})_4$ was 1.08 in DMF and 1.09 in chloroform (CHCl_3). In the case of the 5-isomer, the ratio was 0.98 in DMF and 0.89 in CHCl_3 . According to the conventional classification of the porphyrin spectra⁵⁾ the spectrum of $\text{PH}_2\text{2}(\text{QOH})_4$ can be classified as ethio-type, whereas that of the 5-isomer is phyllo-type.¹⁾ This may be explained in terms of the greater electron-withdrawing character of the 8-quinolinol group in the 5-isomer.⁶⁾

Addition of Cu(II) perchlorate to $\text{PH}_2\text{2}(\text{QOH})_4$ in DMF resulted in biphasic spectral changes, an instantaneous change and a subsequent slow change. The latter change was observable at room temperature only in the presence of a large excess of Cu(II) over the porphyrin. The spectra after the first step are shown in Fig. 2 and they indicate the formation of the free base porphyrin with Cu(II)-chelated 8-quinolinol ($\text{PH}_2\text{2}(\text{QOCu}^+)_4$). The changes of the spectra with the concentration of Cu(II) show that the formation of $\text{PH}_2\text{2}(\text{QOCu}^+)_4$ was incomplete at four-fold excess of Cu(II) over the porphyrin. It was also incomplete at six-fold excess, but was almost complete at eight fold excess. The unexpectedly low stability in Cu(II) chelation by the 8-quinolinol moiety is probably a result of the medium used. We have confirmed that the stability constant of the Cu(II) chelate of 8-quinolinol is much smaller in DMF ($\log K_1 = 1.62$) than in aqueous media.⁷⁾

Fig. 2. Spectra of $\text{PH}_2\text{2}(\text{QOH})_4$ in DMF in the Presence and Absence of Cu(II)

Concentration of $\text{PH}_2\text{2}(\text{QOH})_4$: 1×10^{-6} M (300—480 nm) or 2×10^{-5} M (480—700 nm). Concentrations of Cu(II) were 0 (—), or 4-fold (-----), or 8-fold (.....) excess over $\text{PH}_2\text{2}(\text{QOH})_4$.

Fig. 3. Spectra of $\text{PCu}_2(\text{QOCu}^+)_4$ and $\text{PCu}_2(\text{QOH})_4$ in DMF

$\text{PCu}_2(\text{QOCu}^+)_4$, ----; $\text{PCu}_2(\text{QOH})_4$ (concentration of HClO_4 : 15 mM), —. Concentration of the porphyrin: 1×10^{-6} M (300—480 nm) or 2×10^{-5} M (480—700 nm). Concentration of Cu(II) : 2.6×10^{-5} M (300—480 nm) or 5.2×10^{-4} M (480—700 nm).

Fig. 4. Dependence of the Pseudo-First-Order Rate Constant, k_o , on the Total Concentration of Cu(II) , $[\text{Cu(II)}]_T$

Concentration of the porphyrin: 2×10^{-5} M.

The spectrum after the completion of the second slow spectral change is shown in Fig. 3. The visible bands characteristic of the free base porphyrin were replaced by two bands. Since these bands are assigned as the α and β bands of metalloporphyrin,⁵⁾ the change should indicate the formation of $\text{PCu}_2(\text{QOCu}^+)_4$. The kinetics of the second step in DMF were measured at 30°C by monitoring the absorption at 523 nm. The formation of the metalloporphyrin followed first-order kinetics in the presence of a large excess of Cu(II) . The observed first-order rate constant, k_o , increased linearly with increase of the total concentration of Cu(II) , $[\text{Cu(II)}]_T$, under the conditions used as shown in Fig. 4. The second-order rate constant, k , can be defined by the following equation:

$$d[\text{PCu}_2(\text{QOCu}^+)_4]/dt = k_o[\text{PH}_2\text{2}(\text{QOCu}^+)_4] = k[\text{PH}_2\text{2}(\text{QOCu}^+)_4][\text{Cu(II)}]_T$$

The k value was calculated to be $0.92 \text{ M}^{-1} \text{ s}^{-1}$, almost twice that for the 5-isomer ($0.41 \text{ M}^{-1} \text{ s}^{-1}$).¹⁾

The spectrum of a DMF solution obtained by addition of HClO_4 to $\text{PCu}_2(\text{QOCu}^+)_4$ is shown in Fig. 3. The concentration of HClO_4 was 15 mM. The spectrum can be ascribed to the species $\text{PCu}_2(\text{QOH})_4$. The two weak visible bands characteristic of the metalloporphyrin spectrum were blue-shifted. An increase of the absorbance of the Soret band with the demetallation of the quinolinol moiety was noted. A similar phenomenon was observed with the 5-isomer.

Infrared (IR) and mass spectra (MS) of $\text{PH}_2\text{2}(\text{QOH})_4$ confirmed its structure, as described in the experimental section. The compound and its 5-isomer were practically insoluble in water. The insolubility made it difficult to study the chelation phenomena in aqueous solutions of these bifunctional compounds. Studies of the biological and medical applications were also difficult. For further studies it is desirable to design water-soluble compounds with similar bifunctional nature.

Experimental

2-Formyl-8-quinolinol was prepared by the reported method.⁸⁾ A propionic acid solution (120 ml) of 2-formyl-8-

quinolinol (4.9 g, 28.3 mmol) and pyrrole (1.9 g, 28.3 mmol) was refluxed for 1.5 h. After removal of the solvent, the residue was washed with water, dried and extracted with CHCl_3 . The extract was chromatographed on a silica gel column and 200 mg of a purple crystalline product was obtained from the 2% $\text{MeOH}-\text{CHCl}_3$ eluate. The product was dissolved in 66 ml of EtOH-free CHCl_3 and refluxed for 2 h. After addition of a dry benzene solution (1.3 ml) of 2,3-dichloro-5,6-dicyanobenzoquinone (40 mg), the mixture was refluxed for a further 2 h. Purification by silica gel chromatography afforded 35 mg of *meso*-tetra[2-(8-hydroxyquinolyl)]porphine ($\text{PH}_2\text{2}(\text{QOH})_4$) as purple crystals (yield, 0.6%). MS m/z : 882 (M^+), 738 ($\text{M}^+ - \text{C}_9\text{H}_6\text{NO}$). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3390 (QOH st.), 3290 (NH st.), 1586, 1560, 1497, 1455 (PH_2 C-H st.), 1427, 1309, 1231, 1185, 967 (PH_2 ring def.), 905, 788.

$\text{PH}_2\text{2}(\text{QOH})_4$ was very soluble in DMF, dimethylsulfoxide and 1 M HCl, soluble in CHCl_3 , acetone, AcOEt and dioxane, slightly soluble in MeOH, EtOH, benzene, AcOH, ether and 1 M NaOH and practically insoluble in water.

A Shimadzu UV-240 spectrophotometer, a Hitachi EPI-G3 grating infrared spectrophotometer and a JEOL JMS-D100 mass spectrometer were used throughout the present study.

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