

SYNTHESIS OF PHOSPHORYLCHOLINE-BEARING PORPHINATO-IRON COMPLEXES AND THEIR HEMOLYTIC ACTIVITIES

Etsuo HASEGAWA, Yoh-ichi MATSUSHITA, Kiyoshi ESHIMA
(Res. Lab., Taiho Pharmaceutical Co., Ltd., Tokushima, 771-01) and
Eishun TSUCHIDA (Dep. Polymer Chem., Waseda Univ., Tokyo, 160)

INTRODUCTION It has been found that the heme complexes ($n=1, 14, 18, R'=-CH_3, R=-H$) chelated with hydrophobic imidazole(s) can absorb O_2 reversibly under semiphysiological conditions by incorporating them in a fatty region of liposome.¹ To prepare hemes better-taken in liposome we have tried to control a lipophilic-lipophilic balance of a heme by introducing ω -functionalized alkane groups with keeping a hydrophobic cavity on a porphyrin plane and their hemolytic properties have been studied as one of physiological ones.

SYNTHESES OF PORPHINATO IRONS (Hemins)

The hemins I_n ($R'=-CH_3, R=-COOH$) and II_n ($R'=-CH_3, R=-OP(O)(O)CH_2CH_2N(CH_3)_3$) were synthesized through the reaction scheme illustrated below. II_n s were prepared by phosphocholination of the tetra-ol derivatives using 2-chloro-2-oxo-1,3,2-dioxaphospholane.² I_n ($n=0, 1, 2$) as sodium salts and II_n ($n=1, 10$) were soluble in a neutral aqueous solution.

HEMOLYTIC PROPERTIES

Hemolysis of rat red blood cells by the hemins and protohemin was studied in an isotonic buffered saline (pH 7.4) at 37°C. The reactivity was in the order: Protohemin $> II_{10} > I_{7H} > II_{11}, I_{12}, I_{1H}$ (H means $R'=-H$). The natural hemin had a strong activity.³ The synthetic hemins showed the increase in the activity with their hydrophobicity. However, the carboxyl-bearing hemins had a much weaker activity than the phosphorylcholine-bearing ones. But II_1 was inactive. By measuring gel permeation chromatography it was found that II_{10} forms large aggregates showing its surfactantive property, but I_2 and II_1 forms only a dimer. Various radical scavengers and SOD had no effect on the hemolysis by II_{10} or protohemin, but some ligands (histidine, cysteine etc.) chelating to the iron and catalase retarded the hemolysis. The addition of equimolar bovine serum albumin forbade the hemolysis completely, which forms aggregates

with them. REFERENCES 1) Hasegawa et al., BBRC 105 1416 (1982). 2) Chandrakumar et al., TL 231043 (1982). 3) Chou et al., J. Clin. Inv., 68 672 (1981).

