Oxygen-binding to a Lipophilic Diporphinato Copper–Iron Complex in an Aqueous Medium

Hiroyuki Nishide, Hiromi Maeda, Shen-guo Wang, and Eishun Tsuchida*

Department of Polymer Chemistry, Waseda University, Tokyo 160, Japan

A tetradecyl-substituted diporphinato copper–iron complex, (**1a**), was synthesized and solubilized in an aqueous medium with a surfactant; the oxygen and carbon monoxide binding affinity and the binding rate constants were measured.

There is much interest in the synthesis of a protoporphinato iron complex with oxygen-binding ability in aqueous media. Ward *et al.* have reported that the complex formed between the diporphinato copper–iron species (**1b**) and imidazole formed an oxygen adduct reversibly in benzene and its carbon monoxide binding affinity was much reduced.[1] They proposed that the inert copper porphinato tightly linked to the iron porphinato protects the porphinato iron–oxygen adduct. We also demonstrated reversible oxygen binding and reduced carbon monoxide binding affinity for the (**1c**)–imidazole complex when embedded in polymer films.[2]

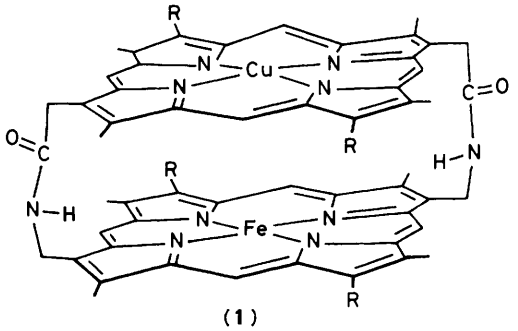
We have recently found that a modified and lipophilic tetraphenylporphinato iron complex of 1-dodecyl imidazole solubilized with a phospholipid or a surfactant binds molecular oxygen reversibly under physiological conditions (at pH 7, 37 °C).[3—7] The porphinato iron complex was thought to be embedded in a bilayer of the phospholipid or incorporated in a micelle of the surfactant and that the hydrophobic environment of the inner region of the bilayer or the micelle protected the oxygen adduct from its irreversible oxidation. This demonstrated oxygen transport properties which are similar to those of the erythrocyte which transports oxygen between the lungs and muscle tissue.

For a more accurate model of a red blood cell a protoporphinato iron complex should be used instead of the tetraphenylporphinato iron complex. The diporphinato copper–

Table 1. The rate constants and the binding-affinity of micellar (**1a**) with oxygen and carbon monoxide.

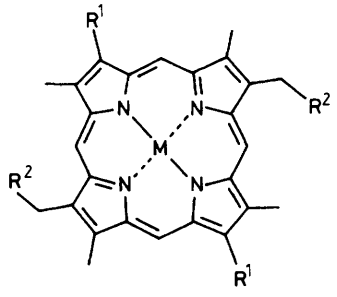
		O_2			CO			
Porphinato iron	Solvent	$k_{on}/M^{-1}s^{-1}$	k_{off}/s^{-1}	$P_{1/2}$/mmHg	$k_{on}/M^{-1}s^{-1}$	k_{off}/s^{-1}	$P_{1/2}$/mmHg	M[a]
(**1a**)	pH 7.4	4.5×10^5	140	36	2.5×10^4	0.05	0.14	257
Chelated heme[b]	pH 7.3	2.6×10^7	47	1.0	4.0×10^6	0.009	0.002	500
(**1b**)[c]	Benzene	2.5×10^5	160	31	2.0×10^4	0.02	0.10	310

[a] $M = [P_{1/2}(O_2)/P_{1/2}(CO)]$. [b] Chelated heme = protoporphinato iron *N*-(3-imidazol-1-ylpropyl)amide methyl ester solubilized by tetradecyltrimethylammonium bromide. From ref. 10. [c] From ref. 1.

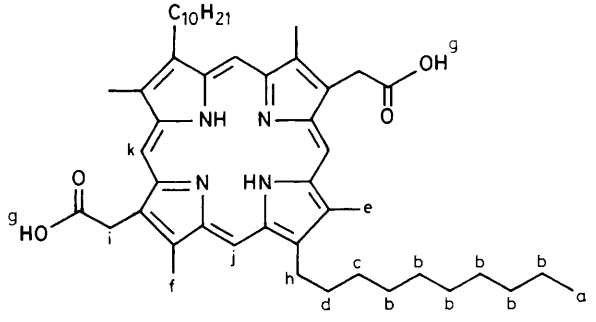


(**1**)

a; R = $C_{10}H_{21}$
b; R = C_5H_{11}
c; R = C_2H_5



(**3**) M = Cu, $R^1 = C_{10}H_{21}$, $R^2 = CO_2C_6H_4NO_2$-*p*
(**4**) M = 2H, $R^1 = C_{10}H_{21}$, $R^2 = NH_2$



(**2**)

iron complexes are characterized by having eight *meso*-hydrogens, which leads to a characteristic visible absorption spectrum and a porphyrin cleavage reaction which is similar to the natural protoporphinato iron complex. In this communication, we report the synthesis of a lipophilic derivative of the diporphinato copper–iron complex (**1a**), which increases the compatibility of (**1**) with the hydrophobic region of the micelle. The oxygen and carbon monoxide binding affinity and the binding rate constants for (**1a**) solubilized in an aqueous medium with a surfactant were measured and compared with other porphinato iron complexes.

Porphyrin (**1a**) was synthesized from 2,7,12,17-tetramethyl-3,13-didecylporphin-8,18-diacetic acid (**2**). The dimethyl ester of (**2**) was prepared from 3-decyl-2-formyl-4-methyl-5-carboxylic acid and 3-methoxycarbonylmethyl-2,4-dimethylpyrrole-5-carboxylic acid; ^1H n.m.r. δ −3.99(2H,s,NH), 0.81(6H,t,H^a), 1.2(24H,m,H^b), 1.45(4H,m,H^c), 2.28(4H,m,H^d), 3.59(6H,s,H^e), 3.63(6H,s,H^f), 3.69(6H,s,H^g), 4.06(4H,t,H^h), 5.01(4H,s,H^i), 10.01(2H,s,H^j), and 10.12(2H,s,H^k); *m/z* = 790. The *p*-nitrophenyl diester derivative of the porphinato copper (**3**) and the diamino derivative (**4**) were derived from (**2**) by modifying the previously reported method.[8,9] Coupling of these in dilute pyridine solution gave (**1a**). Satisfactory elemental analysis of (**1a**) was obtained. U.v.–vis. ($\lambda_{max.}$); 383, 524, and 564 nm. A large R_f value for (**1a**) [0.75/$CHCl_3$: MeOH = 20 : 1 on silica gel; 0.30 for (**1c**)] demonstrated the increased lipophilic nature of (**1a**) compared with (**1c**) as a result of the introduction of the decyl substituents.

The complex of (**1a**) with a lipophilic imidazole such as 1-dodecyl imidazole was solubilized in pH 7.4 phosphate buffer solution with a surfactant such as poly(ethylene oxide) in octyl phenyl ether (*ca.* 1 wt %, which was above the critical micelle concentration of the surfactant). The incorporation of (**1a**) in the micelle was confirmed by g.c. (Sepharose 4B column) monitored by the absorption at 275 and 383 nm based on the surfactant and the (**1a**) complex, respectively. The elution curves coincided with each other, which means that the (**1a**) complex is incorporated in the micelle.

On exposure of the deoxy (**1a**) solution to oxygen, the single peak in the visible absorption spectrum ($\lambda_{max.}$ = 567 nm) was replaced by two peaks ($\lambda_{max.}$ = 534, 569 nm) assigned to the oxygen adduct with isosbestic points at 458 and 581 nm, which correspond to the oxygen adduct formed with an excess of (**1a**) and oxygen. The spectrum of the oxygen adduct changed to that of the CO adduct ($\lambda_{max.}$ 530, 568 nm) on bubbling carbon monoxide through and returned to that of the deoxy complex on bubbling through nitrogen, with isosbestic points at 455 and 479 nm. The oxy–deoxy cycle could be repeated many times at room temperature. This is the first example of reversible oxygen-binding in an aqueous medium for synthetic and non-tetraphenyl-type porphinato iron complexes.

Oxygen and carbon monoxide binding affinity ($P_{1/2}$; pressure required for 50% O_2 or CO binding for the porphinato

iron complex) of the (**1a**) micellar complex was determined by the oxygen and carbon monoxide binding equilibrium curve measurement. The $P_{1/2}$ (O_2) and $P_{1/2}$ (CO) values agreed with the previously reported ones for (**1b**) in benzene[1] (Table 1) and were much reduced compared to those of other synthetic porphinato iron complexes; the M values [$P_{1/2}$ (O_2)/$P_{1/2}$ (CO)] are also given in Table 1.

The oxygen and carbon monoxide binding rate constants were also measured using a flash photolysis method. Both oxygen and carbon monoxide binding rate constants (k_{on}) decreased for the (**1a**) micellar complex probably due to steric hindrance of the porphinato copper cap, which brought about lower gas binding affinity in comparison with other synthetic porphinato iron complexes.

This work was partially supported by a Grant-in-Aid for Research from the Ministry of Education, Science and Culture, Japan.

Received, 2nd January 1985; Com. 008

References

1 B. Ward, C. B. Wang, and C. K. Chang, *J. Am. Chem. Soc.*, 1981, **103**, 5236.
2 E. Tsuchida, H. Nishide, M. Takane, H. Yoshioka, and S-G Wang, *J. Bioinorg. Chem.*, 1985, submitted for publication.
3 E. Tsuchida, H. Nishide, M. Yuasa, E. Hasegawa, and Y. Matsushita, *J. Chem. Soc., Dalton Trans.*, 1984, 1147.
4 E. Tsuchida, H. Nishide, and M. Yuasa, *J. Chem. Soc., Chem. Commun.*, 1984, 96.
5 K. Eshima, M. Yuasa, H. Nishide, and E. Tsuchida, *J. Chem. Soc., Chem. Commun.*, 1985, 130.
6 E. Tsuchida, H. Nishide, M. Yuasa, E. Hasegawa, Y. Matsushita, and K. Eshima, *J. Chem. Soc., Dalton Trans.*, 1985, 275.
7 E. Tsuchida, E. Hasegawa, Y. Matsushita, and K. Eshima, *Inorg. Chim. Acta*, 1984, **93**, L37.
8 C. K. Chang, M. S. Kuo, and C. B. Wang, *J. Heterocycl. Chem.*, 1977, **14**, 943.
9 J. P. Collman, P. Denisevich, Y. Konai, M. Marrocco, C. Koval, and F. C. Anson, *J. Am. Chem. Soc.*, 1980, **102**, 6027.
10 T. G. Traylor and A. P. Berzinis, *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 3171.