Articles

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Catalytic and Stereoselective Activities of Manganese Achiral and Chiral Porphyrins in Dioxygenation of Tryptophan Derivatives

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Received December 7, 1990

Stereoselective tryptophan 2,3-dioxygenase model reactions of the racemic tryptophan derivatives, *N*-acetyl-L(+)- and *N*-acetyl-D(−))-tryptophan methyl esters, were performed with newly synthesized manganese(II or III) complexes of chiral porphyrin which have been characterized by CD spectroscopy. The present reaction included a molecular recognition process and the predominant generation of methyl 2-D(−)-acetamido-3-(2-formamidobenzoyl)propionate achieved to 23.3% enantiomeric excess (ee) in the catalytic system using the manganese complex of $\alpha,\alpha,\alpha,\alpha$-tetrakis[*o*-(L(−)-camphanoylamido)phenyl]porphyrin. Catalytic dioxygenations of tryptophan analogues (3-methylindole, 2,3-dimethylindole, and *N*-methylindole) were also performed with manganese porphyrins and the coordination of the substrate to the manganese porphyrin and the generation of a hydroperoxide intermediate were found to be key steps of the present reaction confirmed by optical absorption, ESR, and NMR measurements of the reaction intermediates.

Introduction

Various metalloporphyrins have been well investigated as a heme-containing oxygenase model in the catalytic insertion of oxygen into organic substrates.[1-10] Especially, manganese porphyrin which has a strong affinity for O_2 with formation of a high-valent Mn^{IV}=O complex shows high activity for the monooxygenation as a cytochrome P-450 model,[2,5] and manganese (or iron) chiral porphyrins have been also used for asymmetric monooxygenations.[6] Tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO) catalyze the oxygenative ring cleavage of either L-tryptophan or its analogues to form a corresponding derivative of L-formylkynurenine;[11] however, there are only a few reports about model systems in which total dioxygen insertion to 3-substituted indoles generating ring-opening products

(1) (a) Hoffman, A. B.; Collins, D. M.; Day, V. W.; Fleischer, E. B.; Srivastava, T. S.; Hoard, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 3620. (b) Latos-Grazynski, L.; Cheng, Ru-Jen; La Mar, G. N.; Balch, A. L. *Ibid.* **1982**, *104*, 5992. (c) Woolery, G. L.; Walters, M. A.; Suslick, K. S.; Powers, L. S.; Spiro, T. G. *Ibid.* **1985**, *107*, 2370. (d) Sabelll, N. H.; Melendres, C. A. *J. Phys. Chem.* **1982**, *86*, 4342. (e) Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427. (f) Collman, J. P.; Brauman, J. I.; Collins, T. J.; Iverson, B. L.; Lang, G.; Pettman, R. B.; Sessler, J. L.; Walters, M. A. *Ibid.* **1983**, *105*, 3038. (g) Hashimoto, T.; Dyer, R. L.; Crossley, M. J.; Baldwin, J. E.; Basolo, F. *Ibid.* **1982**, *104*, 2101. (h) Momenteau, M.; Loock, B.; Lavalette, D.; Tetreau, C.; Mispelter, J. *J. Chem. Soc., Chem. Commun.* **1983**, 962. (i) Larsen, N. G.; Boyd, P. D. W.; Rodgers, S. J.; Wuenschell, G. E.; Koch, C. A.; Rasmussen, S.; Tate, J. R.; Erler, B. S.; Reed, C. A. *J. Am. Chem. Soc.* **1986**, *108*, 6950. (j) Qing-jin, M.; Tondreau, G. A.; Edwards, J. O.; Sweigart, D. A. *J. Chem. Soc., Dalton Trans.* **1985**, 2269. (k) Lexa, D.; Momenteau, M.; Saveant, J. M.; Xu, F. *J. Am. Chem. Soc.* **1986**, *108*, 6942. (l) Burstyn, J. N.; Roe, J. A.; Miksztal, A. R.; Shaevitz, B. A.; Lang, G.; Valentine, J. S. *Ibid.* **1988**, *110*, 1382. (m) Traylor, T. G.; Xu, F. *Ibid.* **1990**, *112*, 178. (n) Balch, A. L.; Chan, Yee-Wai; Olmstead, M. M. *Ibid.* **1985**, *107*, 6510. (o) Sakurai, H. *Chem. Pharm. Bull.* **1976**, *24*, 1686. (p) Tajima, K.; Jinno, J.; Ishizu, K.; Sakurai, H.; Ohya-Nishiguchi, H. *Inorg. Chem.* **1989**, *28*, 709. (q) Tajima, K.; Shigamatsu, M.; Jinno, J.; Kawano, Y.; Mikami, K.; Ishizu, K.; Ohya-Nishiguchi, H. *Biochem. Biophys. Res. Commun.* **1990**, *166*, 924. (r) Yuasa, M.; Nishide, H.; Tsuchida, E. *J. Chem. Soc., Dalton Trans.* **1987**, 2493.

(2) (a) Perree-Fauvet, M.; Gaudemer, A.; Bonvoisin, J.; Girerd, J. J.; Boucly-Goester, C.; Boucly, P. *Inorg. Chem.* **1989**, *28*, 3533. (b) Schappacher, M.; Weiss, R. *Ibid.* **1987**, *26*, 1190. (c) VanAtta, R. B.; Strouce, C. E.; Hanson, L. K.; Valentine, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 1425. (d) Watanabe, T.; Ama, T.; Nakamoto, K. *Inorg. Chem.* **1983**, *22*, 2470. (e) Hoffman, B. M.; Weachler, C. J.; Basolo, F. *J. Am. Chem. Soc.* **1976**, *98*, 5473. (f) Weacher, C. J.; Hoffman, B. M.; Basolo, F. *Ibid.* **1975**, *97*, 5278. (g) Yuan, Lung-Chi; Bruice, T. C. *Ibid.* **1986**, *108*, 1643. (h) Boucher, L. J. *Ibid.* **1970**, *92*, 2725.

(3) (a) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 507. (b) Groves, J. T.; Watanabe, Y. *Ibid.* **1986**, *108*, 7834. (c) Groves, J. T.; Watanabe, Y. *Ibid.* **1988**, *110*, 8443. (d) Collman, J. P.; Hampton, P. D.; Brauman, J. I. *Ibid.* **1990**, *112*, 2977. (e) Collman, J. P.; Hampton, P. D.; Brauman, J. I. *Ibid.* **1990**, *112*, 2986. (f) Balch, A. L.; La Mar, G. N.; Latos-Grazynski, L.; Renner, M. W. *Inorg. Chem.* **1985**, *24*, 2432. (g) Arasasingham, R. D.; Balch, A. L.; Latos-Grazynski, L. *J. Am. Chem. Soc.* **1987**, *109*, 5846. (h) Jorgensen, K. A. *Ibid.* **1987**, *109*, 698. (i) Chevrier, B.; Weiss, R. *Ibid.* **1981**, *103*, 2899. (j) Latos-Grazynski, L.; Cheng, Ru-Jen; La Mar, G. N.; Balch, A. L. *Ibid.* **1981**, *103*, 4270. (k) Castellino, A. J.; Bruice, T. C. *Ibid.* **1988**, *110*, 158. (l) Artaud, I.; Gregoire, N.; Leduc, P.; Mansuy, D. *Ibid.* **1990**, *112*, 6899. (m) Sakurai, H.; Shimomura, S.; Ishizu, K. *Biochem. Biophys. Res. Commun.* **1981**, *101*, 1102. (n) Sakurai, H.; Shimomura, S.; Ishizu, K. *Chem. Pharm. Bull.* **1977**, *25*, 199.

(4) (a) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. (b) Lindsay Smith, J. R.; Sleath, P. R. *J. Chem. Soc., Perkin Trans. 2*, **1983**, 621. (c) Lindsay Smith, J. R.; Mortimer, D. N. *Ibid.* **1986**, 1743. (d) Takagi, S.; Takahashi, E.; Miyamoto, T. K.; Sasaki, Y. *Chem. Lett.* **1986**, 1275. (e) Higuchi, T.; Uzu, S.; Hirobe, M. *J. Am. Chem. Soc.* **1990**, *112*, 7051. (f) Okamoto, T.; Sasaki, K.; Oka, S. *Ibid.* **1988**, *110*, 1187. (g) Sakurai, H.; Kito, M. *Chem. Pharm. Bull.* **1977**, *25*, 2330. (h) Groves, J. T.; Kruper, W. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 7613. (i) Marchon, J. C.; Ramasseul, R. *J. Chem. Soc., Chem. Commun.* **1988**, 298. (j) Aoyama, Y.; Watanabe, T.; Onda, H.; Ogoshi, H. *Tetrahedron Lett.* **1983**, *24*, 1183. (k) Ohkatsu, Y.; Tsuruta, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 188. (l) Kohno, M. *Ibid.* **1986**, *59*, 2053.

(5) (a) Tabushi, I.; Koga, N. *J. Am. Chem. Soc.* **1979**, *101*, 6456. (b) Tabushi, I.; Kodera, M. *Ibid.* **1986**, *108*, 1101. (c) Hill, C. L.; Schardt, B. C. *Ibid.* **1980**, *102*, 6374. (d) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *Ibid.* **1980**, *102*, 6377. (e) Groves, J. T.; Watanabe, Y.; McMurry, T. *Ibid.* **1983**, *105*, 4489. (f) Czernuszewicz, R. S.; Su, Y. O.; Stern, M. K.; Macor, K. A.; Kim, D.; Groves, J. T.; Spiro, T. G. *Ibid.* **1988**, *110*, 4158. (g) Groves, J. T.; Stern, M. K. *Ibid.* **1988**, *110*, 8628. (h) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reine-Artiles, M.; Fort, M.; Mansuy, D. *Ibid.* **1988**, *110*, 8462. (i) Pooter, B. D.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2*, **1985**, 1735. (j) Masui, M.; Tsuchida, K.; Kimata, Y.; Ozaki, S. *Chem. Pharm. Bull.* **1987**, *35*, 3078. (k) Quintana, C. A.; Assink, R. A.; Shelnutt, J. A. *Inorg. Chem.* **1989**, *28*, 3421. (l) Suslick, K. S.; Cook, B. R. *J. Chem. Soc., Chem. Commun.* **1987**, 200. (m) Collman, J. P.; Zhang, X.; Hembre, R. T.; Brauman, J. I. *J. Am. Chem. Soc.* **1990**, *112*, 5356. (n) Collman, J. P.; Brauman, J. I.; Hampton, P. D.; Tanaka, H.; Bohle, D. S.; Hembre, R. T. *Ibid.* **1990**, *112*, 7980.

(6) (a) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (b) Groves, J. T.; Viski, P. *Ibid.* **1989**, *111*, 8537. (c) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (d) Naruta, Y.; Tani, F.; Maruyama, K. *Chem. Lett.* **1989**, 1269. (e) O'Malley, S.; Kodadek, T. *J. Am. Chem. Soc.* **1989**, *111*, 9116.

(7) Yoshida, Z.; Sugimoto, H.; Ogoshi, H. *Adv. Chem. Ser.* **1980**, *191*, 307.

(8) Tajima, K.; Yoshino, M.; Mikami, K.; Edo, T.; Ishizu, K.; Ohya-Nishiguchi, H. *Inorg. Chim. Acta* **1990**, *172*, 83.

(9) Dufour, M. N.; Crumbliss, A. L.; Johnston, G.; Gaudemer, A. *J. Mol. Catal.* **1980**, *7*, 277.

(10) Fujii, T.; Ohta, M.; Kouno, K.; Ono, Y.; Ueda, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4252.

(11) Hayaishi, O.; Rothberg, S.; Mehler, A. H.; Saito, Y. *J. Biol. Chem.* **1957**, *229*, 889.

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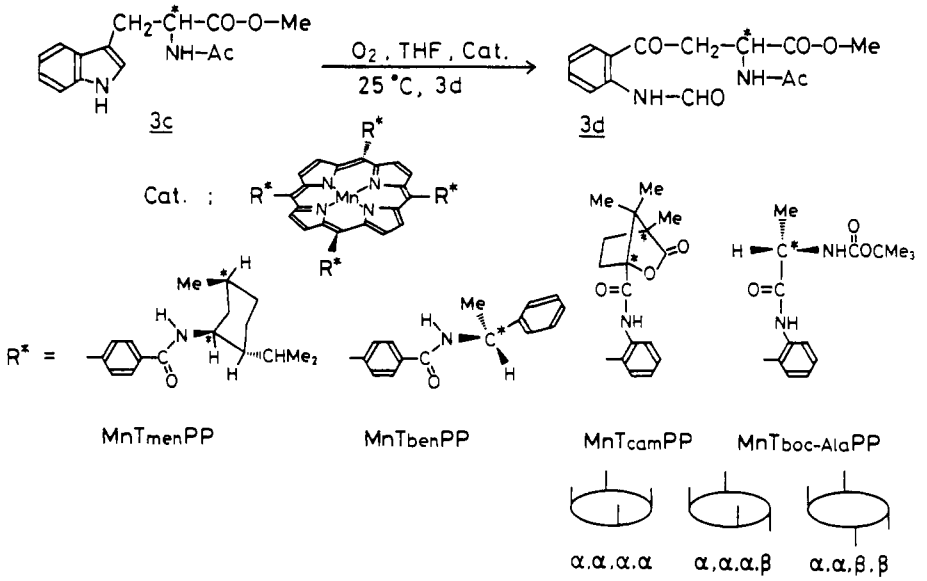
Scheme I



were performed with (tetraphenylporphyrinato)iron ($Fe^{II}TPP$ and $Fe^{III}ClTPP$),[7,8] (tetraphenylporphyrinato)cobalt ($Co^{II}TPP$),[9,10] [bis(salicylidene)ethylenediaminoato]cobalt ($Co^{II}salen$),[12] or manganese phthalocyanine ($Mn^{II}PC$).[13] In order to elucidate the reaction process of TDO or IDO, previous studies have demonstrated that an organic substrate binds to the catalytic site of the dioxygenases to form the metalloenzyme–substrate–O_2 ternary complex which is an important intermediate in the catalytic cycle of the enzymes.[14] Despite extensive studies on the catalytic and activation process of the enzymes, the binding form of tryptophan and O_2 to the active site remains ambiguous due to the lack of clear evidence such as high-resolution X-ray crystal structures of the enzymes.

On the other hand, there is no report dealing with stereoselective dioxygenase model reactions. Expansion of such stereoselective dioxygenase model studies might likely provide useful clues toward an understanding of the reaction process of activation and catalytic oxygenation and of the active-site structure of the enzymes. We wish to report here the stereoselective TDO model reactions with newly synthesized manganese chiral porphyrins, though part of this paper has already appeared.[15] This paper also describes the CD spectra of novel manganese chiral porphyrins. In addition, the reaction intermediates have been investigated by optical absorption, ESR, and ^1H NMR spectroscopy.

Experimental Section

Materials. Tetrahydrofuran (THF), benzene, and other solvents were dried and distilled before use. All other chemical reagents used were of reagent grade. Synthesis of tetraphenylporphyrin free base (H_2TPP) is based on the method described by Adler and co-workers.[16] The preparation of metalloporphyrins consisting of Mn, Fe, or Co were carried out according to the literature.[17]

Synthesis of *N*-Acetyl-L(D or DL)-tryptophan Methyl Esters (3a–c). The tryptophan derivatives, *N*-acetyl-L(D or DL)-tryptophan methyl esters (*3a–3c*) were prepared according to the literature.[18] Acetyltryptophan was prepared from tryptophan with acetic anhydride in a sodium hydroxide solution and was neutralized with sulfuric acid. The methylation of carboxylic acid of acetyltryptophan was performed with thionyl chloride in methanol.

Synthesis of 5,10,15,20-Tetrakis[*p*-(L(−)-menthylcarbamoyl)phenyl]-prophyrin Free Base ($H_2T_{men}PP$) and Manganese Complexes ($Mn^{III}ClT_{men}PP$ and $Mn^{II}T_{men}PP$). $H_2T_{men}PP$ was prepared by the amide linkage reaction of 5,10,15,20-tetrakis(*p*-carboxyphenyl)porphyrin free base (H_2TCPP) with L(−)-menthylamine. H_2TCPP was prepared by Rothemund condensation of *p*-carboxybenzaldehyde with pyrrole in propionic acid according to the literature.[19] A 1.0-g portion (1.3 mmol) of H_2TCPP was dispersed in thionyl chloride (50 mL), and the mixture was refluxed for 4 h with stirring. The residue of 5,10,15,20-tetrakis-[*p*-(chlorocarbonyl)phenyl]porphyrin obtained by the solvent evaporation was dissolved in benzene (50 mL) containing 3 mL of triethylamine. A 4.0-g portion (26 mmol) of L(−)-menthylamine was then added, and the solution was stirred for 3 days. The solvent was evaporated to dryness, and the residue was washed with water. Purification of the crude product by chromatography on an aluminum oxide column (neutral, activity I, 70–230 mesh) eluting with 1:4 dimethylformamide (DMF)/chloroform ($CHCl_3$) afforded $H_2T_{men}PP$ (0.2 g, 12%). ^1H NMR ($CDCl_3$): δ 0.36–1.59 (64 H, m, menthyl), 7.73 (16 H, s, aromatic), 8.73 (8 H, s, pyrrole). UV ($CHCl_3$): λ_{max} 420 nm (ϵ, 180000 cm^{-1} M^{-1}), 517 (11600), 550 (6500), 590 (5200), 646 (3500). Anal. Calcd for $C_{88}H_{114}N_8O_8$: C, 73.92; H, 8.14; N, 7.94. Found: C, 73.67; H, 7.57; N, 7.44. The preparation of $Mn^{III}ClT_{men}PP$ was carried out by heating $H_2T_{men}PP$ with $Mn^{II}Cl_2{\cdot}4H_2O$ in DMF under N_2 and subsequently purifying on an aluminum oxide column eluting with 1:1 DMF/$CHCl_3$. UV for $Mn^{III}ClT_{men}PP$ ($CHCl_3$): λ_{max} 480 nm (ϵ, 57000 cm^{-1} M^{-1}), 581 (10000), 616 (9600). Anal.[20] Calcd for $C_{88}H_{114}ClN_8O_9Mn$: C, 70.27; H, 7.76; N, 7.32. Found: C, 69.61; H, 7.57; N, 7.38. $Mn^{II}T_{men}PP$ was obtained by reduction of manganese(III) porphyrin chloride with $Na_2S_2O_4$ in 1:1:1 $CHCl_3/CH_3OH/H_2O$ under N_2. The color of the organic layer shifted from green to dark blue as the manganese(III) was reduced. The atmosphere in the reaction flask was carefully kept free from oxygen. The organic layer was dried over Na_2SO_4, and the solvent was evaporated and the crude material was recrystallized from DMF/ether. UV for $Mn^{II}T_{men}PP$ ($CHCl_3$): λ_{max} 478 nm, 579, 614. Anal. Calcd for $C_{88}H_{124}N_8O_{14}Mn$: C, 68.32; H, 8.59; N, 6.17. Found: C, 67.20; H, 7.74; N, 7.12.

Synthesis of 5,10,15,20-Tetrakis[*p*-(D(+)-(α-methylbenzyl)carbamoyl)phenyl]porphyrin Free Base ($H_2T_{ben}PP$) and Manganese Complexes ($Mn^{III}ClT_{ben}PP$ and $Mn^{II}T_{ben}PP$). The synthetic procedure for $H_2T_{ben}PP$ was similar to that used for $H_2T_{men}PP$. Coupling H_2TCPP (5.0 g, 6.3 mmol) with D(+)-(α-methylbenzyl)amine (3.8 g, 31.6 mmol) afforded $H_2T_{ben}PP$ (3.0 g, 39%). ^1H NMR (DMSO-d_6): δ 1.68 (12 H, d, CH_3), 5.50 (4 H, q, NH), 7.60 (20 H, m, aromatic), 8.49 (4 H, s), 9.02 (4 H,

(12) (a) Nishinaga, A. *Chem. Lett.* **1975**, 273. (b) Nishinaga, A.; Ohara, H.; Tomita, H.; Matsuura, T. *Tetrahedron Lett.* **1983**, *24*, 213.
(13) Uchida, K.; Soma, M.; Naito, S. *Chem. Lett.* **1978**, 471.
(14) (a) Ishimura, Y.; Nozaki, M.; Hayaishi, O.; Nakamura, T.; Tamura, M.; Yamazaki, I. *J. Biol. Chem.* **1970**, *245*, 3593. (b) Makino, R.; Sakaguchi, K.; Iizuka, T.; Ishimura, Y. *Ibid.* **1980**, *255*, 11883. (c) Kobayashi, K.; Hayashi, K.; Sono, M. *Ibid.* **1989**, *264*, 15280. (d) Sono, M. *Biochemistry* **1989**, *28*, 5400. (e) Sono, M. *Biochemistry* **1990**, *29*, 1451.
(15) Ohkubo, K.; Sagawa, T.; Kuwata, M.; Hata, T.; Ishida, H. *J. Chem. Soc., Chem. Commun.* **1989**, 352.
(16) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
(17) (a) Adler, A. D.; Longo, F. R.; Kampas, F.; Kim, J. *J. Inorg. Nucl. Chem.* **1970**, *32*, 2443. (b) Jones, R. D.; Summerville, D. A.; Basolo, F. *J. Am. Chem. Soc.* **1978**, *100*, 4416.
(18) Balogh-Hergovich, E.; Speier, G. *J. Inorg. Biochem.* **1980**, *13*, 297.
(19) Longo, F. R.; Finarell, M. G.; Kim, J. B. *J. Heterocycl. Chem.* **1969**, *6*, 927.
(20) The numbers of bound waters for new chiral porphyrins are identified by the thermobalance measurement.

s). Anal. Calcd for $C_{80}H_{66}N_8O_4$: C, 77.49; H, 5.47; N, 9.04. Found: C, 77.31; H, 5.59; N, 9.14. The preparation of manganese porphyrin complexes was similar to that used for $Mn^{III}ClT_{men}PP$ and $Mn^{II}T_{men}PP$. UV for $Mn^{III}ClT_{ben}PP$ ($CHCl_3$): λ_{max} 478 nm (ϵ, 66 000 cm^{-1} M^{-1}), 582 (9600), 618 (9500). Anal. Calcd for $C_{80}H_{68}ClN_8O_6Mn$: C, 72.18; H, 5.07; N, 8.63. Found: C, 72.36; H, 5.16; N, 8.44. UV for $Mn^{II}T_{ben}PP$ ($CHCl_3$): λ_{max} 478 nm, 580, 614. Anal. Calcd for $C_{80}H_{82}N_8O_{13}Mn$: C, 67.84; H, 5.20; N, 7.77. Found: C, 67.74; H, 5.83; N, 7.90.

Synthesis of 5,10,15,20-Tetrakis[*o*-(L(−)-camphanoylamido)phenyl]porphyrin Free Base ($H_2T_{cam}PP$) and Manganese Complexes ($Mn^{III}ClT_{cam}PP$ and $Mn^{II}T_{cam}PP$). 5α,10α,15α,20α-Substituted porphyrin ($\alpha,\alpha,\alpha,\alpha$-$H_2T_{cam}PP$) and 5$\alpha$,10$\alpha$,15$\alpha$,20$\beta$ ($\alpha,\alpha,\alpha,\beta$-$H_2T_{cam}PP$) and 5$\alpha$,10$\alpha$,15$\beta$,20$\beta$ isomers ($\alpha,\alpha,\beta,\beta$-$H_2T_{cam}PP$) were prepared according to the literature.[21] 5,10,15,20-Tetrakis(*o*-nitrophenyl)porphyrin free base (H_2TNPP) was prepared by the Rothemund condensation of pyrrole with *o*-nitrobenzaldehyde. Reduction of H_2TNPP with $SnCl_2{\cdot}2H_2O$ in a mixture of concentrated hydrochloric acid and glacial acetic acid afforded 5,10,15,20-tetrakis(*o*-aminophenyl)porphyrin free base (H_2TAPP). The mixture of four H_2TAPP atropisomers was separated by chromatography on a silica-gel column eluting with 1:1 benzene/ether. The amide linkage reaction of H_2TAPP (0.2 g, 0.3 mmol) with L(−)-camphanic acid (0.5 g, 2.5 mmol) and thionyl chloride (30 mL) afforded $H_2T_{cam}PP$ (0.2 g, 52%). ^1H NMR ($CDCl_3$): δ 0.46–1.20 (52 H, m, camphor), 7.08–7.68 (12 H, m), 8.56 (4 H, m, NH), 8.88 (8 H, s, pyrrole). Anal. Calcd for $C_{84}H_{82}N_8O_{12}$: C, 72.29; H, 5.92; N, 8.03. Found: C, 71.96; H, 5.99; N, 7.35. The preparation of $Mn^{III}ClT_{cam}PP$ was carried out by heating the free base porphyrin with manganese(II) chloride and 2,6-lutidine in THF under N_2 and subsequently purifying on a silica-gel column, eluting in turn with $CHCl_3$, and acetone and the solvent were evaporated. The residue was dissolved in $CHCl_3$, and the solution was washed with hydrochloric acid and water. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The manganese(III) porphyrin chloride was recrystallized from benzene/hexane. UV for $Mn^{III}ClT_{cam}PP$ (THF): λ_{max} 480 nm (ϵ, 123 000 cm^{-1} M^{-1}), 578 (13 000), 612 (9000). Anal. Calcd for $C_{84}H_{88}ClN_8O_{16}Mn$: C, 64.30; H, 5.17; N, 7.46. Found: C, 64.84; H, 5.70; N, 7.20. $Mn^{II}T_{cam}PP$ was obtained by reduction of manganese(III) porphyrin chloride with $Na_2S_2O_4$ in 1:1:1 THF/benzene/H_2O under N_2. UV for $Mn^{II}T_{cam}PP$ ($CHCl_3$): λ_{max} 439 nm, 470, 574, 608. Anal. Calcd for $C_{84}H_{92}N_8O_{18}Mn$: C, 65.63; H, 6.49; N, 6.17. Found: C, 64.81, H, 5.96; N, 7.20.

Synthesis of 5,10,15,20-Tetrakis[*o*-((*tert*-butyloxycarbonyl)-L(−)-alaninamino)phenyl]porphyrin Free Base ($H_2T_{boc\text{-}Ala}PP$) and Manganese Complexes ($Mn^{III}ClT_{boc\text{-}Ala}PP$ and $Mn^{II}T_{boc\text{-}Ala}PP$). (*tert*-Butyloxycarbonyl)-L(−)-alanine (0.3 g, 1.6 mmol) was dissolved in THF (2 mL). This solution was cooled to 268 K under N_2, and *N*-methylmorpholine (0.18 mL, 1.6 mmol) and isobutylchloroformate (0.21 mL, 1.6 mmol) was added. The resulting mixture was then reacted with H_2TAPP (0.27 g, 0.4 mmol) and *N*-methylmorpholine (0.18 mL, 1.6 mmol) in THF with stirring at 268 K for 1 h, and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated to dryness, and the residue was dissolved in ethylacetate and washed in turn with 5% sodium hydrogen carbonate, water, 1 N hydrochloric acid, and water. Then the organic phase was dried over anhydrous sodium sulfate and the crude product was purified by chromatography on a silica-gel column; eluting with 1:1 benzene/ether afforded $H_2T_{boc\text{-}Ala}PP$ (0.17 g, 32%). ^1H NMR ($CDCl_3$): δ 0–1.50 (48 H, m, CH_3), 3.25 (4 H, s), 5.08 (4 H, s, NH), 7.14–7.71 (16 H, m, aromatic), 8.65 (8 H, m, pyrrole). UV ($CHCl_3$): λ_{max} 420 nm (ϵ 358 000 cm^{-1} M^{-1}), 515 (12 000), 549 (5900), 588 (7000), 644 (2300). Anal. Calcd for $C_{76}H_{92}N_{12}O_{15}$: C, 64.57; H, 6.48; N, 11.89. Found: C, 64.83; H, 6.55; N, 10.10. The preparation of manganese porphyrin complexes was similar to that used for $Mn^{III}ClT_{cam}PP$ and $Mn^{II}T_{cam}PP$. UV for $Mn^{III}ClT_{boc\text{-}Ala}PP$ ($CHCl_3$): UV λ_{max} 480 nm, 578, 612. Anal. Calcd for $C_{76}H_{84}ClN_{12}O_{12}Mn$: C, 62.45; H, 5.74; N, 11.26. Found: C, 63.04; H, 5.85; N, 11.61. UV for $Mn^{II}T_{boc\text{-}Ala}PP$ ($CHCl_3$): UV λ_{max} 476 nm, 574, 604. Anal. Calcd for $C_{76}H_{88}N_{12}O_{13}Mn$: C, 64.02; H, 6.09; N, 10.48. Found: C, 63.02; H, 6.12; N, 11.60.

Physical Measurements. UV–visible spectroscopy for the coordination process of O_2 (or the substrates) to $Mn^{II}TPP$ (or $Mn^{III}ClTPP$) was measured by using a Hitachi 150-20 spectrophotometer. ESR spectra were recorded for the interacting system of O_2, substrate, and the metalloporphyrin at 293 K in solution and 77 K in the frozen state with a JEOL spectrometer (MgO powder doped with Mn^{II} was used as a standard with 100-kHz field modulation). ^1H NMR spectra of the reaction intermediates were recorded on a JEOL MH-100 spectrometer in $CDCl_3$ or DMSO-d_6 solution containing TMS. CD spectroscopic measurements for the reactants, products, and chiral catalysts in the stereoselective reaction were obtained with a JASCO data processor DP-500 attached to the J-500 spectropolarimeter. Experimental conditions for CD (210–400 nm) were as follows: time constant, 32 s; scan speed, 10 nm min^{-1}; sensitivity, 0.5 mdeg cm^{-1}; accumulation times, 4; temperature, 298 K. Other details are shown in the figures.

Table I. R_f Values and UV Absorptions of Tryptophan Analogues (**1a**, **2a**, and **3a–c**) and Dioxygenated Products (**1b**, **2b**, and **3d**)

	R_f	developing solvent	I/nm (ϵ/cm^{-1} M^{-1})[a]
1a	0.67	benzene/ether/ *n*-heptane (1:1:1)	290 (3820)
			282 (4590)
1b	0.43		318 (4450)
			259 (12400)
2a	0.71	benzene/ether (9:1)	290 (6020)
			283 (6820)
2b	0.33		322 (4410)
			266 (9370)
3a–c	0.41	ethyl acetate	290 (5230)
	(0.61)	acetone/ether (1:1)	281 (6140)
3d	0.23		320 (3620)
	(0.52)		258 (9460)

[a] UV absorptions in MeOH.

Table II. Oxygenation of 3-Methylindole (**1a**) by Metalloporphyrins[a]

cat.	conv/%[b]	**1a** (consumed)/ cat.	yield/%[c]	**1b**/cat.
$Mn^{III}ClTPP$	63.5	6.4	17.4	1.7
$Mn^{II}TPP$	90.2	9.0	15.4	1.5
$Fe^{III}ClTPP$	22.6	2.3	6.1	0.6
$Fe^{II}TPP$	77.8	7.8	8.6	0.8
$Co^{III}ClTPP$	15.4	1.5	trace	
$Co^{II}TPP$	47.6	4.8	20.2	2.0

[a] The reactions were carried out in the tetrahydrofuran (10 mL) solutions containing **1a** (5.0×10^{-4} mol) and the metalloporphyrin complex (5.0×10^{-5} mol) in an O_2 atmosphere at 298 K for 1 day. [b] Calculated on the basis of **1a**. [c] Yield of *o*-formamidoacetophenone (**1b**).

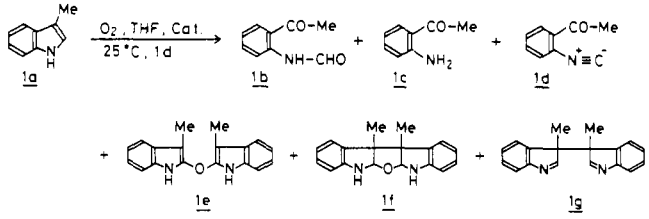
Dioxygenation of Tryptophan Analogues and Derivatives Catalyzed by Metalloporphyrins. All the tryptophan analogues such as 3-methylindole (*1a*), 2,3-dimethylindole (*2a*), and *N*-methylindole (*4a*) and tryptophan derivatives (*3a–c*) were found to contain no dioxygenation products before reaction. Blank experiments were performed in the absence of metalloporphyrin and revealed that no dioxygenation products were present before reactions except the case of *2a*.[22] The oxygenations of the tryptophan analogues or derivatives by the metalloporphyrins were carried out under atmospheric dioxygen at room temperature in THF for 1 or 3 days. The ring-opening products were identified with an authentic samples by ^1H NMR, IR, MS, and UV spectroscopy. The amounts of unreacted substrates and the products were determined spectrophotometrically after separating them from the reaction mixtures by TLC on silica gel (Merck F254). R_f values and UV absorptions for the substrates (*1a–3c*) and the ring-opening products (*1b–3d*) are listed in Table I.

Results and Discussion

Dioxygenation of 3-Methylindole by Metalloporphyrins. In order to determine the optimal conditions of dioxygenation, the experimental results for the dioxygenation of 3-methylindole (*1a*) by metalloporphyrins consisting of Mn, Fe, or Co are given in Table II. In the presence of excess 3-methylindole (*1a*) (Table II, conditions in footnote *a*), conversions of the reaction decreased from ca. 90% with $Mn^{II}TPP$ to ca. 15% with $Co^{III}ClTPP$. The dioxygenation of 3-methylindole (*1a*) produced a considerable amount of *o*-formamidoacetophenone (*1b*) as the major ring-opening product with negligibly small amounts of ring-opening byproducts such as *o*-aminoacetophenone (*1c*) and *o*-isocyanoacetophenone (*1d*), together with small amounts of the other products (not ring-opening ones such as *1e–1g*), as shown in eq 1. The results shown in Table II demonstrate that conversions of the reaction with manganese porphyrins were larger than those with the other metalloporphyrins. Higher conversion was observed

(21) Takagi, S.; Miyamoto, T. K.; Sasaki, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 447.

(22) **2a** can be oxidized to the ring-opening product (**2b**) without metalloporphyrin (yield of **2b** = 8.3%).



(1)

in the system containing M(II) complexes rather than M(III) porphyrin chlorides, probably due to the two open coordination sites of the former for the interaction with substrate or O_2.

Spectroscopic Measurements of Reaction Intermediates for Dioxygenation of Tryptophan Analogues by Manganese Porphyrins. In order to examine the catalytic and activation process of the oxygenation, the reaction intermediates have been investigated by optical absorption, ESR, and ^1H NMR spectroscopy.

The addition of 3-methylindole (*1a*) to $Mn^{III}ClTPP$ in THF at room temperature in the absence of O_2 resulted in the spectral change of the visible Soret band absorption (Figure 1). This broadening shift in the Soret band at 474 nm in Figure 1 may be assigned to the six-coordinate complex (3-methylindole)-$Mn^{III}ClTPP$, since the similar results of the visible spectral changes in the Soret band by addition of tryptophan to TDO (or IDO) have been reported.[14] When a degassed THF solution of $Mn^{II}TPP$ was continuously bubbled with O_2 at room temperature, the solution showed rapid spectral changes of the absorption decrease at 413, 433, 568, and 605 nm with newly appeared absorption bands at 370, 392, 469, 574, and 615 nm. The red-shifted Soret and Q bands of [$Mn^{II}TPP + O_2$] were the same as those observed for the spectra of the five-coordinate complex, $Mn^{III}ClTPP$. This result indicates that O_2 coordinates quickly to the $Mn^{II}TPP$ to form the five-coordinate complex, $Mn^{III}TPP(O_2^-)$.[5a,e,17b] When *1a* was added to an O_2-saturated THF solution of $Mn^{II}TPP$, the broadening shift in the Soret band similar to the spectra shown in Figure 1 was observed. The extent of the absorption decrease at 474 nm in [$Mn^{II}TPP + O_2 +$ *1a*] ($\Delta Abs = 0.22$) was larger than that in [$Mn^{III}ClTPP +$ *1a*] ($\Delta Abs = 0.10$; see Figure 1). This was consistent with the catalytic activities, in which the M(II) porphyrins obtained higher conversions than those by the M(III) porphyrin chlorides (see Table II). Tajima et al.[8] reported the detection of a metal–oxygen–substrate ternary intermediate complex in the model dioxygenase reaction system composed of $Fe^{III}ClTPP$, 3-methylindole, and alkaline reagent. Nishinaga et al.[12] and Uchida et al.[13] also reported the detection of a substrate–metal–oxygen ternary intermediate complex in the TDO model reaction systems using Co^{II}salen and $Mn^{II}PC$, respectively. Taking into consideration the results obtained from electronic spectroscopy measurements of the reaction system, we assume that *1a* may coordinate to $Mn^{III}TPP(O_2^-)$ to form a ternary complex, (3-methylindole)$Mn^{III}TPP(O_2^-)$, in our present nonaqueous reaction system. Similar visible spectral changes were also observed by mixing of indole derivatives such as 3-methylindole (*1a*), 2,3-dimethylindole (*2a*), or N-methylindole (*4a*), with $Mn^{II}TPP$ in O_2-saturated benzene (Figure 2). From these spectral changes and the reaction results (conversion and yield of ring-opening products summarized in Table III), the following features seem worthy of note: The remarkable Soret band (474 nm) change of *2a* which has two electron-releasing CH_3 groups indicates that *2a* coordinates most readily to $Mn^{III}TPP(O_2^-)$ so as to accelerate the subsequent dioxygenation reaction with the highest conversion and yield for *2a*. In this respect, the ease of the substrate coordination to $Mn^{III}TPP(O_2^-)$, which is corresponding to the extent of the Soret band change, well reflects the order of conversion or product yield in Table III. *4a* might not coordinate to $Mn^{III}TPP(O_2^-)$ and has no reactivity. So far, we have never isolated the substrate binding complex of manganese porphyrin from the reaction mixture; however, coordination of the indole derivative to $Mn^{III}TPP(O_2^-)$ is assumed to occur through the direct binding of the nitrogen atom in the indole ring to the central metal of the porphyrin. Thus, the coordination of the indole

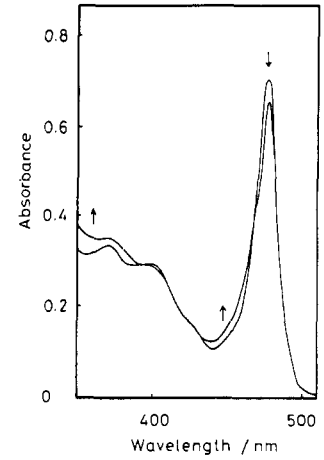


Figure 1. Visible spectra changes observed by the addition of 3-methylindole (5.0×10^{-2} mol dm^{-3}) to $Mn^{III}ClTPP$ (5.0×10^{-6} mol dm^{-3}) in THF.

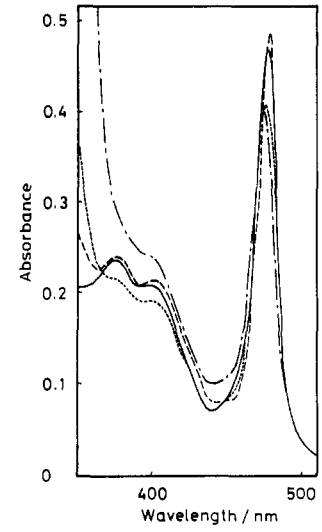


Figure 2. Visible spectra changes observed by the addition of indole derivatives (1.0×10^{-1} mol dm^{-3}) to $Mn^{II}TPP$ (5.0×10^{-5} mol dm^{-3}) in benzene; MnTPP + O_2 (—), MnTPP + O_2 + **1a** (···), MnTPP + O_2 + **2a** (-·-), MnTPP + O_2 + **4a** (- - -).

Table III. Oxygenation of Indole Derivatives (**1a–4a**) by $Mn^{II}TPP$[a]

substrate	conv/%	yield (**1b–4b**)/%
1a	90.2	15.4
2a[b]	100.0	44.4
3a	76.7	32.1
4a	0[c]	0[c]

[a] The reaction conditions are the same as in Table II. [b] **2a** can be oxidized to the ring-opening product without the catalyst (yield of **2b** = 8.3%). [c] For 48 h.

derivative to the manganese porphyrin is necessary for the present reaction to proceed.

The ESR spectrum observed for the O_2-saturated and frozen THF solution of $Mn^{III}ClTPP$ and 3-methylindole showed the presence of free-radical species, as shown in Figure 3A, in which two signals were observed at $g = 2.004$ and 2.016. The relatively strong ESR signals at 2.004 and 2.016 were also observed for the mixture of $Mn^{II}TPP$ and *1a* with O_2 in THF (Figure 3B). On the other hand, a single ESR signal at $g = 2.004$ was detected for the O_2-saturated THF solution of $Mn^{II}TPP$. The analogous ESR spectrum was also detected after addition of *N*-methylindole (*4a*) to the O_2-saturated THF solution of $Mn^{II}TPP$, as shown in Figure 3C, but the oxygenative cleavage product did not form under the same conditions (compare Table III). Therefore, the ESR signal at $g = 2.004$ in the present oxygenation systems containing *1a* might not be attributable to the active species. Also,

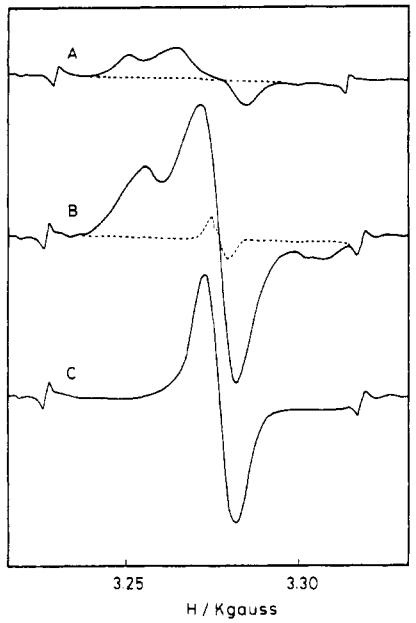


Figure 3. ESR spectra recorded for a frozen mixture of indole derivative (1.0 mol dm^{-3}), manganese porphyrin (1.0×10^{-2} mol dm^{-3}), and O_2 in THF at 77 K: (A) MnClTPP + O_2 + **1a** (—), MnClTPP + O_2 (···) and MnClTPP + **1a** (···); (B) MnTPP + O_2 + **1a** (—) and MnTPP + O_2 (···); (C) MnTPP + O_2 + **4a**.

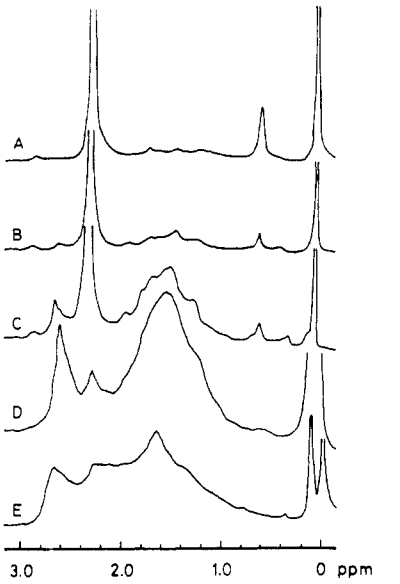


Figure 4. NMR methyl-signal change in the reaction of 3-methylindole (**1a**) with $Mn^{II}TPP$ and O_2 (the same NMR spectra were given by the reaction with $Mn^{III}ClTPP$): (A) 20 min; (B) 40 min; (C) 6 h; (D) 1 day after mixing; (E) 3 h after addition of CF_3CO_2H to D.

neither the ESR spectrum of the O_2-saturated and frozen THF solution of $Mn^{III}ClTPP$ nor that of the degassed and frozen THF solution of $Mn^{II}TPP$ showed a signal around $g = 2.0$. Although the degassed mixture of $Mn^{III}ClTPP$ and *1a* in THF indicated no ESR signal around $g = 2.0$, the ESR signal observed at $g = 2.016$ as shown in Figure 3A,B might be attributable to the active species connected with *1a* in the present oxygenation systems: a ternary complex (3-methylindole$^{\bullet}$)MnXTPP (X = Cl or O_2^-) and/or a indolyl peroxide complex, (3-methylindolyl-OO$^{\bullet}$)-MnXTPP. The former might be generated by the electron transfer from indole to the metalloporphyrin. The larger ESR signal intensity of the free-radical species in Figure 3B as compared with that in Figure 3A well reflected the higher conversion obtained by the M(II) porphyrins as compared with that obtained by the M(III) porphyrin chlorides (see Table II).

When the dioxygenation of 3-methylindole by $Mn^{II}TPP$ or $Mn^{III}ClTPP$ in $CDCl_3$ was carried out in an NMR tube at 298 K, the methyl signal of *1a* (2.35 ppm) disappeared gradually with the reaction time (Figure 4). The methyl resonances at 2.35 and 2.74 ppm in Figure 4 were assigned as the methyl groups of the substrate (*1a*) and the ring-opening product (*1b*). Another resonance at 1.60 ppm in Figure 4A was assigned as the methyl signal of indolyl hydroperoxide by Dufour et al.,[9] though the present NMR spectra were slightly broader because of the paramagnetic manganese porphyrin/O_2 system. Disappearance of the resonance at 1.60 ppm was observed by addition of CF_3CO_2H to the reaction mixtures at 333 K.

Scheme II

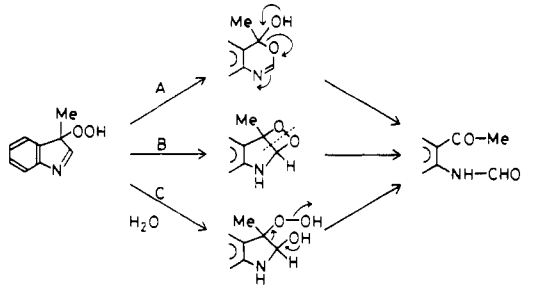


Table IV. Oxygenation of *1a* by Manganese(II) Porphyrins[a]

Mn^{II} porphyrin	conv/%	yield (**1b**)/%
$Mn^{II}TPP$	90.2	15.4
$Mn^{II}T_{men}PP$	52.4	21.7
$Mn^{II}T_{boc\text{-}Ala}PP$ ($\alpha,\alpha,\alpha,\alpha$)	39.3	16.1
$Mn^{II}T_{boc\text{-}Ala}PP$ ($\alpha,\alpha,\beta,\beta$)	69.1	23.8

[a] The reactions were carried out at 298 K under the following conditions: **1a** (5.0×10^{-4} mol) and $Mn^{II}TPP$ (5.0×10^{-5} mol) in THF (10 mL) for 1 day; **1a** (1.0×10^{-4} mol) and $Mn^{II}T_{men}PP$ (or $Mn^{II}T_{boc\text{-}Ala}PP$) ($1.0 \times 10^{-5}$ mol) in THF (5 mL) for 15 h.

From the arguments mentioned above, the present oxygenations of an alkyl-substituted indole by the manganese porphyrins may proceed as follows: The coordination of the substrate to manganese porphyrin complex, (3-methylindole)$Mn^{III}ClTPP$ and (3-methylindole)$Mn^{III}TPP(O_2^-)$, was confirmed by the UV measurements of the reaction system. Then, the generation of the free-radical species, (3-methylindole$^{\bullet}$)MnXTPP (X = Cl or O_2^-) and/or (3-methylindolyl-OO$^{\bullet}$)MnXTPP, might be suggested by the ESR measurement. At present, the accurate formation process of the O_2-inserted indolyl hydroperoxide is still ambiguous; however, the intermolecular reaction of two ternary complexes [(3-methylindole)MnTPP(O_2)–(3-methylindole)MnTPP(O_2)] or the reaction of the indole radical with free molecular dioxygen is thought to result in the generation of the hydroperoxide which was detected by NMR spectroscopy. The hydroperoxide once formed gives the ring-opening product via the intramolecular reactions in Scheme II. In Scheme II, path A (Criegee type[23,24] seems most plausible because path B (dioxetane type) is thermodynamically difficult[24] and because the path C is discarded in the present nonaqueous reaction.

Dioxygenation of 3-Methylindole by Manganese Chiral Porphyrins. The catalytic activities of manganese chiral porphyrins ($Mn^{II}T_{men}PP$, $Mn^{II}T_{boc\text{-}Ala}PP$ ($\alpha,\alpha,\alpha,\alpha$), and $Mn^{II}T_{boc\text{-}Ala}PP$ ($\alpha,\alpha,\beta,\beta$)) were examined in the ring-opening dioxygenation of 3-methylindole (*1a*) before discussing their catalytic abilities for stereoselective dioxygenations, and the experimental results are shown in Table IV. The conversion of the reaction with manganese achiral porphyrin ($Mn^{II}TPP$) was larger than those with the manganese chiral porphyrins, but the ratios of the main *1b* product yield to conversion, yield/conv, in the case of the manganese chiral porphyrins were found larger than that in the case of the manganese achiral porphyrin ($Mn^{II}TPP$). This result is attributable to the bulkiness of the chiral ligands. The bulky ligands may hinder the coordination of the substrate to the metalloporphyrin but prevent the generation of dimeric products (e.g.

(23) Muto, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7381.
(24) Fraser, M. S.; Hamilton, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 4203.

Table V. Stereoselective Oxygenation of the *N*-Acetyl-DL-tryptophan Methyl esters (**3c**) Catalyzed by Manganese Chiral Porphyrins[a]

	substrate (3c)		product (3d)	
Mn chiral porphyrin	conv/ %	ee[b] (config)/%	yield/ %	ee (config)/%
$Mn^{II}T_{men}PP$	29	17.4 (L)	2.4	14.9 (L)
$Mn^{III}ClT_{men}PP$	18	2.6 (L)	1.0	11.0 (L)
$Mn^{II}T_{ben}PP$	45	3.1 (D)	5.9	9.7 (D)
$Mn^{III}ClT_{ben}PP$	37	14.1 (D)	1.3	9.7 (D)
$Mn^{II}T_{cam}PP$ ($\alpha,\alpha,\alpha,\alpha$)	9.5	8.6 (D)	6.1	23.3 (D)
$Mn^{II}T_{cam}PP$ ($\alpha,\alpha,\alpha,\beta$)	15	8.4 (D)	8.5	1.2 (D)
$Mn^{III}ClT_{cam}PP$ ($\alpha,\alpha,\alpha,\beta$)	8.8	19.3 (D)	0.9	8.8 (D)
$Mn^{II}T_{cam}PP$ ($\alpha,\alpha,\beta,\beta$)	13	7.6 (D)	10.4	5.8 (D)
$Mn^{II}T_{boc\text{-}Ala}PP$ ($\alpha,\alpha,\alpha,\alpha$)	0		0	
$Mn^{II}T_{boc\text{-}Ala}PP$ ($\alpha,\alpha,\beta,\beta$)	0		0	

[a] The reactions were carried out by keeping THF (5 mL) solutions containing the racemate **3c** (1.0×10^{-4} mol) and the manganese porphyrin complex (1.0×10^{-5} mol) in an O_2 atmosphere at 298 K for 3 days. [b] Enantiomeric excess of the accumulated enantiomer of **3c**.

1e–g) via intermolecular reactions between intermediates.

Stereoselective Dioxygenation of Racemic Tryptophan Derivatives by Manganese Chiral Porphyrins. The stereoselectivities of several newly synthesized manganese chiral porphyrins were determined in the dioxygenations of racemic tryptophan derivatives (*3c*). The conversions, yields, and their enantiomeric excesses are summarized in Table V. As Table V indicates, the consumption values of *3c* by the equatorial type porphyrins ($MnT_{men}PP$ and $MnT_{ben}PP$) were found to be more remarkable than those by the axial type porphyrins ($\alpha,\alpha,\alpha,\alpha$-$MnT_{cam}PP$, $\alpha,\alpha,\alpha,\beta$-$MnT_{cam}PP$, $\alpha,\alpha,\beta,\beta$-$MnT_{cam}PP$, $\alpha,\alpha,\alpha,\alpha$-$MnT_{boc\text{-}Ala}PP$, and $\alpha,\alpha,\beta,\beta$-$MnT_{boc\text{-}Ala}PP$), probably because the axial ligand moiety in the last group of the catalysts hindered the coordination of the substrate (*3c*). Such a steric hindrance of the axial ligand moiety is most notable in the cases of the two $Mn^{II}T_{boc\text{-}Ala}PP$ complexes. Among the chiral Mn(II and III) complexes possessing the chiral porphyrin ligands of $T_{men}PP$, $T_{ben}PP$, and $\alpha,\alpha,\alpha,\beta$-$T_{cam}PP$, the higher conversions were observed in the low-valent Mn(II) complexes having two open sites for the coordination of the substrate. CD spectra (λ_{max} 220 nm) of unreacted *3c* were measured by separation from the reaction mixtures with TLC after the reaction catalyzed by $Mn^{II}T_{ben}PP$ and $Mn^{II}T_{men}PP$ (Figure 5A–C). The predominant consumption of the D(−) isomer (*3b*) of the substrate by $Mn^{II}T_{ben}PP$ catalyst led to the accumulation of the L(+) isomer (*3a*). On the other hand, $Mn^{II}T_{men}PP$ predominantly consumed the L(+) isomer (*3a*) of the substrate, and the selective generation of the L(+) isomer of the product (*3d*) (λ_{max} 250 nm in Figure 5C) was identified. These stereoselective dioxygenations of *3c* with the chiral catalysts resulted in optical yields falling in the range 2.6–19.3% ee for the consumption of *3c* and of 1.2–23.3% ee for the formation of *3d* (see Table V). Among the equatorial and axial manganese(II,III) porphyrins, $Mn^{II}T_{men}PP$ (in the early catalysts) and $\alpha,\alpha,\alpha,\alpha$-$Mn^{II}T_{cam}PP$ and $\alpha,\alpha,\alpha,\beta$-$Mn^{III}ClT_{cam}PP$ (in the later ones) were found to be most effective for the substrate (*3c*) stereoselectivities and the chiral product (*3d*) formations. The maximum substrate stereoselectivity was 19.3% ee in the dioxygenation with $\alpha,\alpha,\alpha,\beta$-$Mn^{III}ClT_{cam}PP$, and the highest optical yield for the generation of the chiral product *3d* was 23.3% ee in the reaction with $\alpha,\alpha,\alpha,\alpha$-$Mn^{II}T_{cam}PP$. The observed stereoselectivity seems to indicate that oxygenation occurs via indole complexation, and this observation is useful for elucidating the catalytic process as described previously. It is noteworthy here that the product stereoselectivities were different from the substrate stereoselectivities. The substrate stereoselection by the catalyst only occurs during the formation process of the substrate–catalyst complex, but the stereoselection of the chiral product by the catalyst might be enhanced (or weakened) by the subsequent intermolecular reaction of the substrate–metal–O_2 ternary complexes.

It seems also of interest to notice how the chirality of the manganese chiral porphyrins contributes to their stereoselective abilities. The CD spectra of $MnT_{men}PP$, $MnT_{ben}PP$, and $MnT_{cam}PP$ are depicted in Figure 6. The CD spectral intensities of a Soret-region extremum of $Mn^{III}ClT_{men}PP$ and $Mn^{III}ClT_{ben}PP$

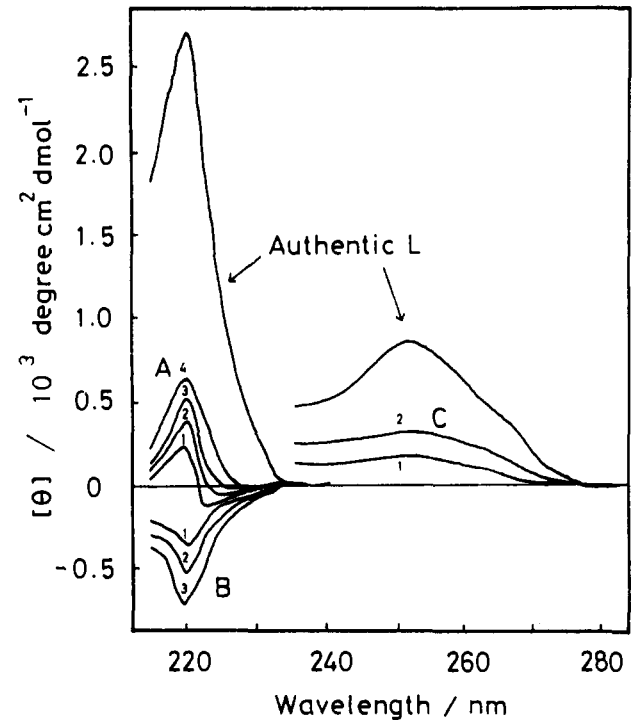


Figure 5. CD spectra of **1c** (A, B) and **2c** (C) separated from the reaction mixtures after dioxygenating **3c** with the chiral porphyrin complexes, $Mn^{II}T_{ben}PP$ (A) and $Mn^{II}T_{men}PP$ (B, C). Conversion: (A) (1) 0%, (2) 24.5%, (3) 32.1%, (4) 41.9%; (B) (1) 19.5%, (2) 24.7%, (3) 25.7%. Yield: (C) (1) 0%, (2) 2.4%.

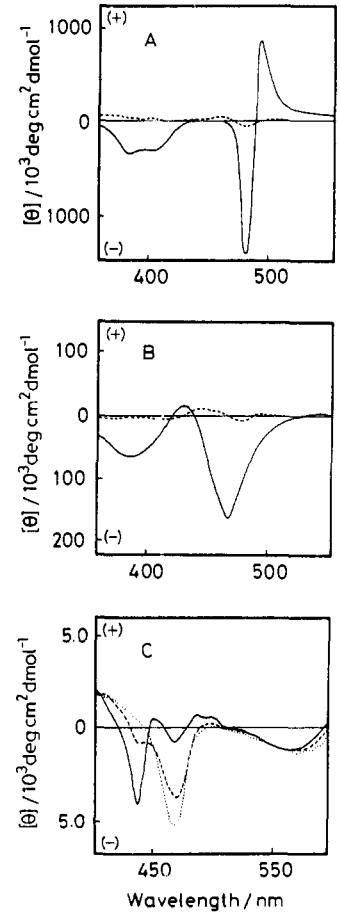


Figure 6. CD spectra of (A) $Mn^{II}T_{men}PP$ (···) and $Mn^{III}ClT_{men}PP$ (—), (B) $Mn^{II}T_{ben}PP$ (···) and $Mn^{III}ClT_{ben}PP$ (—), and (C) $Mn^{II}T_{cam}PP$ ($\alpha,\alpha,\alpha,\alpha$ (—), $\alpha,\alpha,\alpha,\beta$ (- - -), $\alpha,\alpha,\beta,\beta$ (···)).

(in Figure 6A or B) are larger than those of the Mn(II) complexes because of the increase of molecular asymmetry by introduction of chloride as the axial ligand. The considerable difference in the intensities of CD spectra between Mn(II) and Mn(III) complexes of $MnT_{men}PP$ or $MnT_{ben}PP$ did not reflect the same extent of the stereoselectivities between the Mn(II) and Mn(III) complexes possessing identical chiral parts (denoted as men or ben in Table V). The chirality of the L(-)-menthyl or D(+)-α-menthylbenzyl moiety of the porphyrin seems to directly influence their stereoselective abilities for the coordination of the substrate to the manganese chiral porphyrins, though the chiral substituents of these porphyrins are in the para positions of the TPP structures. The change in the chiral ligand of the three atropisomers of $Mn^{II}T_{cam}PP$ from the α,α,β,β-type to the α,α,α,α-one via the α,α,α,β-one increased the intensities of the CD spectra at 440 nm (with a gradual decrease of the ellipticity at 460 nm) by changing the extent of molecular asymmetry around the central metal of the porphyrin (Figure 6C). Such a ligand change from the α,α,β,β-type to the α,α,α,α-one is not associated with the substrate stereoselectivity of $Mn^{II}T_{cam}PP$ having the identical L(-)-camphanoyl moiety; however, we assume that the appropriate orientation of the chiral L(-)-camphanoyl portion in α,α,α,α-$Mn^{II}T_{cam}PP$ for the coordination sites of the substrate would result in not only effective substrate stereoselection but also high enantiomeric excess of the ring-opening product via the Criegee rearrangement reaction.

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Resonance Raman and Magnetic Resonance Spectroscopic Characterization of the Fe(I), Fe(II), Fe(III), and Fe(IV) Oxidation States of Fe(2-TMPyP)$^{n+}$(aq)

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Received November 27, 1991

Four oxidation states of aqueous *meso*-5,10,15,20-tetrakis(2-*N*-methylpyridyl)porphinatoiron {Fe(2-TMPyP)(aq)} have been characterized at pH 9 and 12 via resonance Raman (RR), NMR, and ESR spectroscopic methods. These pH values were chosen because they are below and above the pK_a values of the Fe(II) (11.2), Fe(III) (11.0), and Fe(IV) (10.0) complexes. The 2-$TMPyP^{2+}$ ligand stabilizes four iron oxidation states, I–IV, in aqueous solution. The porphyrin core size marker band frequencies in the RR spectra are consistent with the metal ion radius increasing from Fe(IV) to Fe(II), but decreasing again for Fe(I). The Fe(I) core size is smaller than that of the Fe(II) species because Fe(I) is four-coordinate and low spin, whereas Fe(II) is five-coordinate and high spin. ESR data of the highly reduced complex ($g_\perp$ = 2.32 and $g_\parallel$ = 2.00) clearly demonstrate that Fe(II) reduction gives Fe(I) and not the porphyrin π-anion radical at pH 9 and 12. This is the first Fe(I) complex to be observed in aqueous solution, and the potentials of the Fe(II/I) couples (-0.740 V at pH 9 and -0.763 V at pH 12) are among the most positive of any yet observed for a porphinato complex. The first observation of a Fe^{II}–OH stretch in a model heme complex is reported and assigned to a band at 464 cm^{-1} on the basis of its 20-cm^{-1} downshift in $H_2{}^{18}O$. The Fe^{II}–OH adduct is five-coordinate and high spin on the basis of its RR and NMR spectra. The Fe(IV/III) potentials at pH 9 and 12 are among the least positive ever reported for porphyrin complexes. For solutions with pH > p$K_{a[Fe(IV)]}$, an Fe(IV) complex can be chemically or electrochemically generated and is stable for hours at room temperature. The low-frequency RR spectrum of this species exhibits an Fe^{IV}=O stretch at 763 cm^{-1}, which was assigned on the basis of its 31-cm^{-1} downshift in $H_2{}^{18}O$. This Fe(IV) complex gains its stability from coordination of the ferryl iron by an axial hydroxide ligand. For solutions with pH < p$K_{a[Fe(IV)]}$, a transient Fe(IV) species is generated. At both pH values, the Fe(IV) complexes are converted to porphyrin π-cation radical species at 120 K, as evidenced by their broad ESR lines near g = 2. However, the RR data indicate that an e_g ground state is thermally accessible and that the primary species in the room temperature solution is an Fe(IV) complex. The six-coordinate Fe(IV) species shows an upfield β-pyrrole ^2H NMR isotropic shift (-9.9 ppm) that is consistent with previously characterized six-coordinate porphinatoiron(IV) complexes in nonaqueous solution. Resonance Raman, NMR, and ESR data for the various oxidation states and states of axial ligation in the Fe(2-TMPyP) complexes suggest that the unique ability of this porphyrin ligand to stabilize both Fe(I) and Fe(IV) oxidation states is primarily due to the electrostatic influence of the *N*-methylpyridinium moieties at the porphyrin periphery, as opposed to perturbation of the interaction between metal ion and tetraarylporphyrin π orbitals. The stabilization of such a wide range of oxidation states is unprecedented in iron porphyrin chemistry and demonstrates that it is possible to modulate the coordination and redox chemistry of model hemes through variations in the electrostatic potential in which it resides without severely perturbing the intrinsic properties of the metalloporphine moiety.

Introduction

The rich chemistry exhibited by heme proteins has spawned numerous studies involving model heme complexes. These porphinato complexes have been employed as structural and reactivity models to relate heme structure and environment to reactivity, and to its control, as well as to tailor catalytic oxidants for synthetic purposes.

Two aspects of heme reactivity that are influenced by its protein environment are its oxidation/reduction potentials and the thermodynamics and kinetics of axial ligation. As axial ligand binding constants for the heme are nearly always a function of solution acidity or basicity, the axial coordination chemistry of aqueous porphinatoiron complexes with water and hydroxide ion is fundamental to understanding the coordination chemistry of aqueous heme proteins. Recent accounts from this laboratory reported the first observations of axial Fe^{III}–OH stretching vibrations in a model heme complex.[1] For solutions in which 5 < pH < 11, the principal species is the five-coordinate hydroxo-*meso*-5,10,15,20-tetrakis(2-*N*-methylpyridyl)porphinatoiron(III) [(Fe(2-TMPyP)$(OH)^{4+}$(aq)] complex, whereas at alkaline pH (pH > 11) the dominant species is the bis(hydroxo) species [Fe(2-TMPyP)$(OH)_2{}^{3+}$(aq)].[1] Recent work by Chen et al.[2] suggested that, as well as facilitating the formation of these monomeric hydroxoiron(III) complexes, the water-soluble porphyrin ligand in this complex exhibits the remarkable ability to stabilize Fe(I) and Fe(IV) in aqueous alkaline solution at ambient temperature. Moreover, the stabilities of most of these species are sufficient to permit their characterization via resonance Raman

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(1) (a) Reed, R. A.; Rodgers, K. R.; Kushmeider, K.; Su, Y. O.; Spiro, T. G. *Inorg. Chem.* **1990**, *29*, 2881. (b) Rodgers, K. R.; Reed, R. A.; Su, Y. O.; Spiro, T. G. *New J. Chem.*, in press.
(2) Chen, S.-M.; Sun, P.-J.; Su, Y. O. *J. Electroanal. Chem.* **1990**, *294*, 361.

0020-1669/92/1331-2688$03.00/0